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Evaluation of Pharmacotherapies for Alcoholic Liver Disease: A Retrospective Real-World Evidence Study

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Abstract

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Background: Ursodeoxycholic acid (UDCA), a hepatoprotective agent demonstrates several beneficial effects on liver biochemistry measures and thus, it might be useful for the management of Alcoholic liver disease (ALD).

Objective: To evaluate the pharmacotherapies for ALD using retrospective real-world evidence.

Methods: In this retrospective study, the Electronic Medical Records (EMRs) of patients with ALD who were prescribed various pharmacotherapies between January 2021 and April 2021 at two Indian healthcare settings were reviewed. The effectiveness outcomes were assessed in terms of mean difference and proportion of patients showing improvement in the levels of liver enzymes (Aspartate aminotransferase [AST], Alanine aminotransferase [ALT] and γ -glutamyl transferase [GGT]) and conjugated bilirubin from baseline to 30-days follow-up.

Results: A total of 298 patients were included and divided into two study groups - scientific and herbal groups. The scientific group included patients prescribed with drugs like UDCA, pentoxifylline, ademetonine, metadoxine, and nutritional supplementation. The herbal group included patients prescribed with four different Herbal Preparations. Of 193 patients in the scientific group, a majority (76.7%; n=148/193) of the patients received UDCA; of these, 107 patients' data were available at the 30-days follow-up. In the herbal group (n=105), a majority (62.9%; n=66/105) of the patients received Herbal Preparation 1, and 78 patients had data at follow-up. The elevated levels of liver enzymes (AST, ALT, GGT) at baseline were significantly reduced ($p < 0.05$) at follow-up in patients prescribed with UDCA vs. Herbal Preparation 1. The change from baseline to 30 days in conjugated bilirubin was significantly higher in the UDCA vs. Herbal Preparation 1 (-45.2% vs. -33.5%, $p < 0.001$). There was considerable improvement in the proportion of patients with elevated AST and ALT in the UDCA group. No serious adverse events were reported in either of the groups. **Conclusions:** The present study demonstrates that UDCA and Herbal Preparation 1 are majorly used in the management of ALD. UDCA has shown a substantial hepatoprotective effect as evident by significant improvements in the liver biochemistry of ALD patients as compared to the Herbal Preparation 1. Overall, the data from the current study suggests the use of UDCA as an initial therapy for ALD patients with altered liver enzymes

Introduction

Alcoholic liver disease (ALD) is the most prevalent chronic liver disease globally, with a prevalence of 94.8 per 10000 individuals^[1]. ALD has multifactorial pathophysiology comprising a broad spectrum of hepatic lesions. ALD can be divided into three major clinicopathologic classes: alcoholic steatosis, alcoholic hepatitis, and alcoholic cirrhosis^[2]. The disease progresses in a well-recognized pattern that begins with Alcoholic fatty liver (AFL), characterized by steatosis (accumulation of fat in the hepatocytes) to a more acute and inflammatory 'Alcoholic steatohepatitis (ASH)'. This can further lead to fibrosis with excessive deposition of extracellular matrix proteins which can progress to cirrhosis, manifested by pronounced liver scarring, vascular changes, and subsequently liver failure^[3]. Severe ASH (with or without cirrhosis) can progress to alcoholic hepatitis, an acute clinical presentation of ALD, which is linked to liver failure and mortality^[2,3]. Histologic cholestasis (reduction or stoppage of bile flow) and jaundice may occur across the entire spectrum of ALD or may be observed independent of significant steatosis, hepatitis, or cirrhosis^[4]. About 50% of the patients ensue a state of irretrievable liver damage or cirrhosis, which might result in several complications such as portal hypertension leading to upper gastrointestinal hemorrhage, ascites, splenomegaly, and other entities of chronic liver disease^[5].

The diagnosis of ALD is clinically challenging as patients may not show any clinical signs at an early stage, or patients may have co-existing risk factors for non-alcoholic fatty liver disease such as obesity and diabetes, which further complicate the diagnosis of ALD^[6]. ALD is suspected in patients with a history of considerable consumption of alcohol and abnormal Liver function tests (LFTs) including serum bilirubin, conjugated bilirubin, Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Aspartate aminotransferase (AST), and γ -glutamyl transferase (GGT)^[7,8].

ALT and AST are five times elevated than the Upper limit of normal (ULN) in mild alcohol-related liver injuries, whereas more than 10 to 15 times elevated than the ULN in moderate and severe cases, respectively, representing acute liver injury^[9]. GGT is elevated even in the early stages of ALD and alcoholic fatty liver. Hence, the estimation of LFTs helps to diagnose and stage the severity of ALD^[10,11].

The prevention and treatment of ALD require a multidisciplinary approach for managing alcohol use disorder (AUD), including nutritional, psychological, pharmacological, and surgical interventions^[12]. The European Association for the Study of the Liver (EASL) clinical guidelines state that no specific pharmacological therapy has demonstrated unequivocal efficacy for alcoholic cirrhosis^[13].

There are still no Food and Drug Administration (FDA) approved pharmacological or nutritional interventions for treating ALD^[14]. There are no guidelines defined for the management of ALD in India. The effectiveness of several pharmacotherapeutic agents has been investigated including propylthiouracil, colchicine, and polyenyl

phosphatidylcholine however, literature has evidenced no significant advantage of these therapies as compared to placebo^[15-17].

Ursodeoxycholic acid (UDCA), a hepatoprotective agent, has been known to improve clinical and biochemical signs of cirrhosis and delay the onset of disease in patients with primary biliary cirrhosis (PBC). UDCA has received approval by the Central Drugs Standard Control Organization (CDSCO), India, for the management of various liver disorders like chronic cholestatic liver disease (CCLD), PBC, and gall stones, and by the U.S. FDA for the treatment of patients with PBC in 2016^[18,19]. Thereafter, UDCA has been increasingly used for the treatment of other CCLD conditions^[20,21]. Splendid study found supporting evidence of UDCA use in CCLD, which is a known etiology for ALD, viral hepatitis, and NAFLD^[22]. UDCA has shown a significant reduction of elevated liver enzymes and bilirubin levels in ALD patients^[23]. Few studies have reported that Herbal Preparation 1, an herbal preparation, is used in the treatment of liver disorders.^[24] The role of Herbal preparation 1 for ALD is still uncertain as some studies have reported its beneficial role while others have documented no improvement in clinical outcome or liver biochemistry^[25-27]. Further, Herbal Preparation 2 has also been majorly used, as it demonstrated significant survival benefits in patients with chronic liver disease^[28]. However, contrasting results with no confirmed benefits from this preparation are also present in the literature^[29, 30].

Despite the prominent burden of ALD on liver-related morbidity and mortality, very little progress has been made in developing promising pharmacotherapies over the last few decades compared to the tremendous advances in other liver diseases^[12]. In India, there is a scarcity of studies on the clinical profile and management of ALD. The current study evaluated the pharmacotherapies for ALD using retrospective real-world evidence.

Methods

This was a retrospective observational study with data collected from the Electronic Medical Records (EMRs) of patients with ALD visiting health care settings (n=2) from two Indian states (Gujarat and Rajasthan) from January 2021 to April 2021.

Study population

Patients aged >18 years, who were diagnosed with ALD and had received different pharmacotherapies, were included. Patient data were collected from the hospital outpatient database. Patients who had at least one baseline visit, and one follow-up visit after 30 days were included. Patients were required to have at least two LFT values, one at the baseline visit and another at the follow-up visit. Patients with liver disease not related to alcohol or clinically decompensated cirrhosis were excluded. (Figure 1)

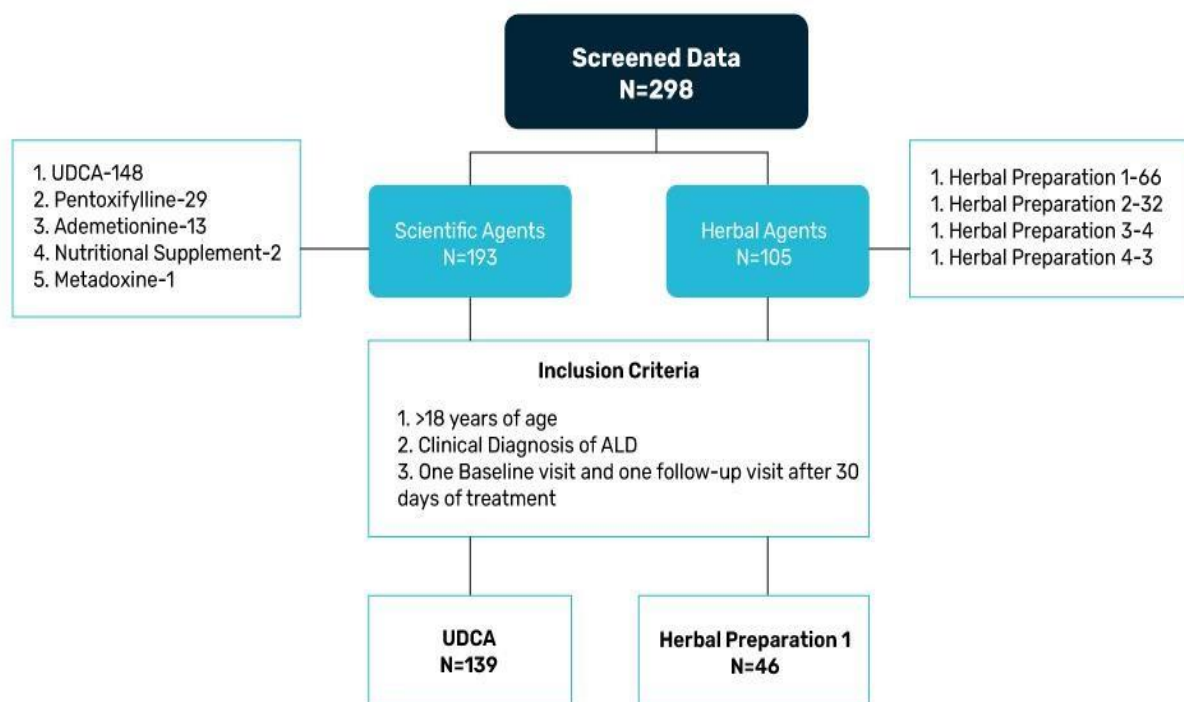


Figure 1: Data inclusion flow-chart

Treatments

The patients were divided into two groups, i.e., scientific group and herbal group, based on the pharmacotherapy prescribed. The scientific group included patients prescribed with drugs like UDCA, pentoxifylline, ademetonine, nutritional supplement (thiamine hydrochloride, magnesium oxide, zinc sulphate, pyridoxine hydrochloride, folic acid, selenium dioxide and copper sulphate), and metadoxine, which are approved by CDSCO for the management of other conditions^[21]. The herbal group included patients prescribed Herbal Preparation 1 (Capparis spinosa, Cichorium intybus, Solanum nigrum, Terminalia arjuna, Cassia occidentalis, Achillea millefolium, Tamarix gallica), Herbal Preparation 2 (Silymarin), Herbal Preparation 3 (Boerhavia diffusa, Tephrosia purpurea, Emblica officinalis, Piper nigrum) and Herbal Preparation 4 (Terminalia chebula, Terminalia bellirica, Emblica officinalis, Asphaltum, Commiphora mukul, Plumbago zeylanica, Picrorhiza kurroa).

Outcomes

The effectiveness outcomes were assessed as the decrease in the elevated baseline conjugated bilirubin levels, decrease

in elevated baseline liver enzymes including AST, ALT, and GGT after 30 days of treatment, and the proportion of patients who showed improvement in biochemical parameters in both the groups. Safety was assessed in terms of reported Adverse events (AEs) during the treatment period (30 days).

Statistical Analysis

The Kolmogorov Smirnov test was used to assess the normality of the data. Continuous normal data were expressed as mean and Standard deviation (SD), continuous skewed data by the median and Inter-quartile range (IQR), and categorical data as numbers and percentages. The differences between the continuous variables were analyzed by independent sample t-test/ Mann-Whitney U-test and between the categorical variables by the Chi-square test. The p-value <0.05 was considered to report statistical significance.

Ethical Statement

This was a retrospective study and the existing medical records that were available as of the date of EC submission were used for the study without any additional prospective components for research purposes. The patients' confidentiality was maintained using anonymized and de-identified data at the source level. Hence, the process did not necessitate the obligation to obtain informed consent^[31]. Accordingly, permission for ICF waiver was obtained from an Independent Ethics Committee before initiation of data collection process for this study.

Results

Baseline Characteristics

A total of 298 EMRs of ALD patients were screened for the study. The patients were divided into scientific and herbal groups based on the medications prescribed (Figure 1). In the scientific group, UDCA was prescribed to the majority (76.7%; 148/193) of the patients, followed by pentoxifylline (15.0%; 29/193), ademetionine (6.7%; 13/193), nutritional supplement (1.0%; 2/193), and metadoxine (0.5%; 1/193). In the herbal group, Herbal Preparation 1 (62.9%; 66/105) was prescribed to the majority of the patients, followed by Herbal Preparation 2 (30.5%; 32/105), Herbal Preparation 3 (3.8%; 4/105), and Herbal Preparation 4 (2.9%; 3/105). The complete follow-up data were missing for many patients and mostly available for patients prescribed UDCA (n=139) and Herbal Preparation 1 (n=46); hence they were considered for further statistical analysis.

The mean age of patients in the study was found to be 43.51 ± 9.82 years and 44.09 ± 10.03 years in UDCA and Herbal Preparation 1 groups, respectively. All the patients in this analysis were males. Overall, the baseline characteristics were comparable between the groups. Some of the patients in the study were known to have comorbid conditions like diabetes mellitus, hypertension, and obesity (Table 1).

Table 1: Baseline characteristics

Parameters	UDCA (N=148)	Herbal Preparation 1 (N=66)	Herbal Preparation 2 (N=32)	Pentoxifylline (N=29)	Ademetionine (N=13)	Nutritional supplement (N=2)	Metadoxine (N=1)	Herbal Preparation 3 (N=4)	Herbal Preparation 4 (N=3)
Age in years, mean (SD)	43.51 (9.82)	44.09 (10.03)	45.41 (7.91)	40.62 (6.81)	47.65 (8.07)	42.64 (2.84)	40.50 (0)	43.01 (8.09)	42.32 (3.65)
Gender, n (%)									
Male	148 (100)	66 (100)	32 (100)	29 (100)	13 (100)	2 (100)	1 (100)	4 (0)	3 (100)
Weight (Kg), mean (SD)	65.53 (7.22)	62.33 (5.81)	61.56 (6.24)	67.97 (5.98)	68.48 (11.14)	65.54 (3.54)	60.28 (0)	61.32 (7.21)	64.82 (4.32)
Height (cm), mean (SD)	169.43 (6.12)	170.48 (2.93)	170.50 (3.84)	169.97 (5.24)	165.58 (7.03)	170.32 (4.65)	168.00 (0)	161.33 (4.98)	168.42 (4.87)
BMI (kg/m ²), mean (SD)	22.82 (2.13)	21.45 (1.95)	21.22 (2.41)	23.51 (1.52)	24.98 (3.91)	22.64 (2.63)	21.50 (0)	21.36 (2.01)	22.43 (3.54)
Pulse (bpm), mean (SD)	80.07 (6.17)	78.87 (5.21)	79.22 (4.59)	82.59 (5.81)	84.53 (10.10)	82.44 (1.89)	80.00 (0)	77 (6.32)	78.99 (5.63)
SBP (mmHg), mean (SD)	133.38 (7.73)	128.15 (7.30)	127.84 (5.64)	136.69 (7.04)	131.35 (6.84)	128.77 (4.45)	120.00 (0)	130.43 (5.33)	129.89 (6.25)
DBP (mmHg), mean (SD)	84.10 (4.69)	82.02 (3.60)	80.34 (3.38)	85.69 (4.50)	84.02 (5.83)	82.42 (2.22)	80.00 (0)	80.22 (3.89)	83.64 (4.87)
Comorbidities (n)									
Hypertensive	11	3	0	13	2	-	-	-	-
Diabetic	3	7	11	1	2	1	-	-	-
Obese	1	1	0	4	-	-	-	-	-
Concomitant medications (n)									
Rifaximin	27	-	-	9	-	-	-	-	-
Pantoprazole	41	1	-	15	-	-	-	1	-
Propranolol	31	2	-	9	-	-	-	-	-
Metformin	9	-	11	-	4	1	-	-	-
Aceclofenac	-	1	-	-	-	-	-	-	-
Omega 3	-	24	28	6	-	-	-	1	-
Glimepiride	7	-	-	-	-	-	-	-	-
Telmisartan	-	-	-	-	3	-	-	-	-

BMI: Body Mass Index; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure; UDCA: Ursodeoxycholic acid

Effectiveness

The results of the present study demonstrated significant improvement ($p < 0.05$) in the mean value of AST (93.83 IU/L at baseline vs. 58.15 IU/L after 30 days) in the UDCA group as compared with the Herbal Preparation 1 group (from 74.37 IU/L at baseline to 56.78 IU/L); the corresponding reductions in the AST levels were 38.00% and 23.65%, respectively. In addition, the improvement in AST levels at follow-up was found to be 30.10% in the UDCA group compared to 17.80% in the Herbal Preparation 1 group (Figure 2).

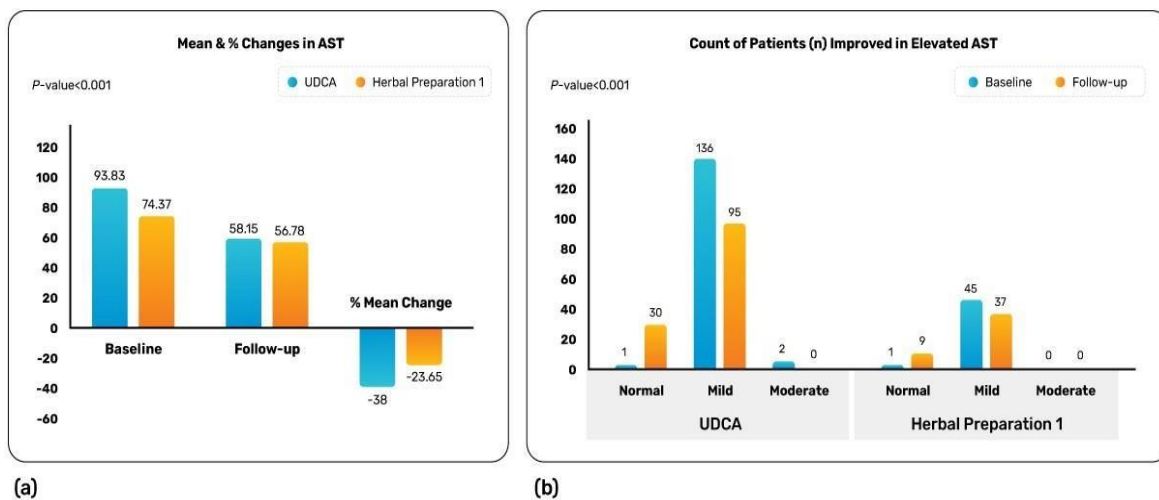


Figure 2: (a) Mean change in AST levels from baseline to follow-up visit; (b) Proportion of patients with elevated and normal levels of AST

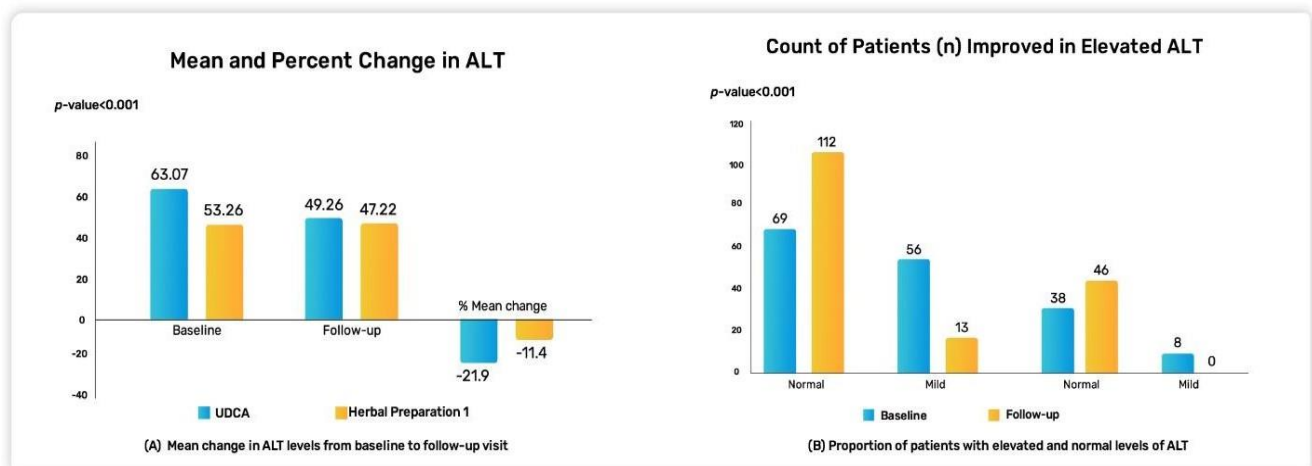


Figure 3: (a) Mean change in ALT levels from baseline to follow-up visit; (b) Proportion of patients with elevated and normal levels of ALT

Similarly, UDCA showed significant ($p<0.05$) improvement in mean values of ALT with a reduction of 21.9% compared to 11.4% in the Herbal Preparation 1 group. Around 77% of patients were shifted to normal levels from elevated ALT levels with UDCA while in the Herbal Preparation 1 group, there was no significant difference (Figure 3). There was a significant ($p<0.001$) reduction from baseline to day 30 in the elevated levels of GGT by 49.65% in the UDCA group compared with 2.52% in the Herbal Preparation 1 group (Figure 4).

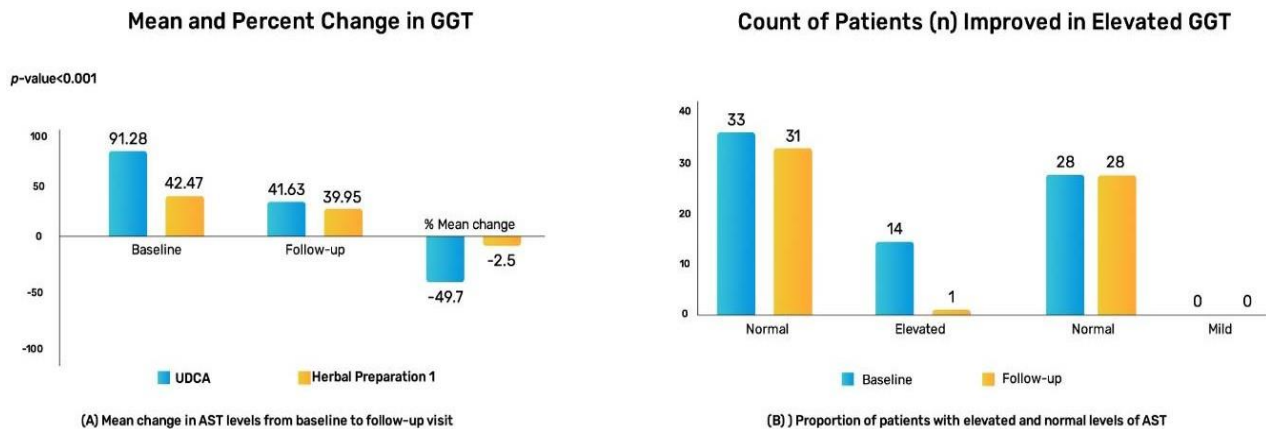


Figure 4: (a) Mean change in GGT levels from baseline to follow-up visit; (b) Proportion of patients with elevated and normal levels of GGT

The study also demonstrated a significant ($p<0.001$) reduction in the elevated levels of conjugated bilirubin levels (45.2% vs. 33.5%) for UDCA vs. Herbal Preparation 1 groups, respectively, after 30 days of treatment (Figure 5).

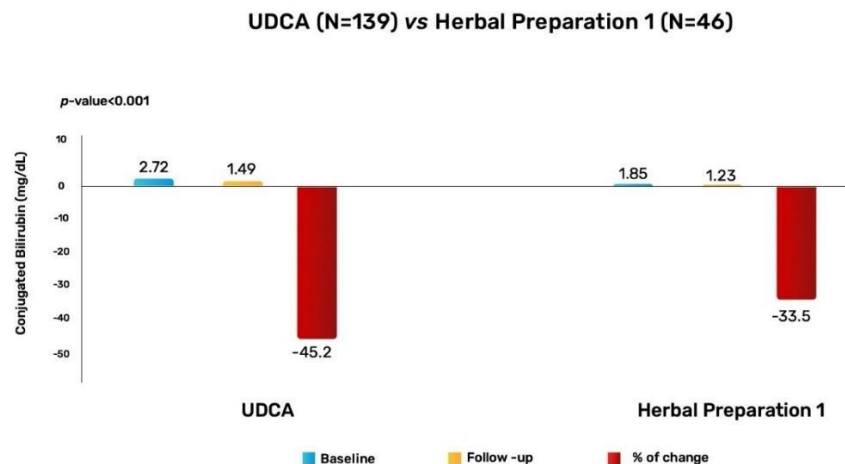


Figure 5: Mean change in the conjugated bilirubin levels from baseline to day 30

In corollary, the use of UDCA showed a significant reduction ($p<0.001$) in the ALP levels (304.16 IU/L at baseline vs. 282.26 IU/L after 30 days) as compared to Herbal Preparation 1 (248.09 IU/L at baseline vs. 267.70 IU/L after 30 days); the corresponding reductions were 7.2% and 5.8%, respectively.

There was not much improvement seen in the liver enzymes and conjugated bilirubin levels in the patients using other drugs like pentoxifylline, Herbal Preparation 2, Herbal Preparation 4, *etc.*, whose follow-up data were available.

Tolerability

Both UDCA and Herbal Preparation 1 were well tolerated in ALD patients. In the UDCA group ($n=139$), AEs like headache, diarrhea, back pain, nausea, dizziness, indigestion, vomiting were reported. While in the Herbal Preparation 1 group ($n=46$), AEs like headache, dizziness, dryness of the mouth, abdominal pain were reported. The reported adverse effects were not found to be statistically significant between the groups. These adverse effects cannot be attributed to current pharmacotherapies, as the patients also received concomitant medications during the treatment period. There were few similar adverse events reported in the patients using other drugs like pentoxifylline, Herbal Preparation 2, Herbal Preparation 4, *etc.*, whose follow-up data was available.

Discussion

The current study evaluated the pharmacotherapies for ALD, and it has been observed that various medications are used for the management of ALD, including scientific drugs like UDCA, pentoxifylline, ademetonine, nutritional supplement, and metadoxine and herbal drugs like Herbal Preparation 1, Herbal Preparation 2, Herbal Preparation 3, and Herbal Preparation 4. Since most of the patients did not have the complete data at follow-up and considering that UDCA and Herbal Preparation 1 were majorly used, a head-to-head comparison was done to evaluate the effectiveness and safety of UDCA and Herbal Preparation 1 in ALD patients. The current study demonstrated that administration of UDCA for 30 days was efficacious in ALD. There was a significant decline in the elevated levels of conjugated bilirubin, and liver enzymes like ALT, AST, GGT, and ALP in the UDCA group as compared to the Herbal Preparation 1 group. The improvement of these biochemical parameters is required to manage ALD and delay the disease progression.

UDCA has several mechanisms of action that target one or more pathogenetic processes of cholestatic liver disease, including stimulation of impaired biliary secretion, detoxification of hydrophobic bile acids, protection of injured cholangiocytes, against toxic effects of bile acids, and inhibition of apoptosis of hepatocytes^[32].

Long-term consumption of alcohol is associated with cholestasis^[33]. The patients with ALD frequently manifest clinical or histologic evidence of cholestasis; therefore, UDCA therapy might prove beneficial. In a study conducted in patients ($n=12$) with alcoholic cirrhosis, UDCA (15 mg/kg) showed a significant reduction in bilirubin, GGT, and ALT levels after four weeks when compared with placebo. However, no significant difference was observed in ALP, prothrombin time, and urea. Further, the authors postulated that UDCA might reduce the proceeding hepatic damage

in ALD despite continued alcohol abuse^[23]. Preobrazhenskiĭ and colleagues reported similar findings following a 6-month study with UDCA. Lawate *et al.*, characterized the profiles of patients taking UDCA for chronic cholestatic liver diseases and determined its effectiveness, tolerability, and compliance in the study population^[34, 22]. The findings of the study demonstrated that most of the patients (89.1%) were diagnosed with Intrahepatic cholestasis (IHC), and ALD was the most common etiology of IHC. UDCA was reported to be the preferred drug owing to its efficacy (73.39%), as standard of care (62.5%), and good tolerability (45.56%). Moreover, within four weeks of treatment initiation, a reduction in healthcare visits, inpatient hospitalization, and days off work was observed.^[22] However, a Cochrane analysis on pentoxifylline in severe alcoholic hepatitis concluded that pentoxifylline is superior to placebo, and further data are needed for firm conclusions to be drawn^[35].

Herbal Preparation 1, an ayurvedic liver preparation, has shown hepatoprotective effects through significantly improving Child-Pugh score, ascites, ALT, AST, total bilirubin, albumin, and prothrombin time as compared with placebo after six months in liver cirrhotic patients (n=36). This protective effect of Herbal Preparation 1 was attributed to the diuretic, anti-inflammatory, anti-oxidative, and immunomodulating properties of the component herbs.^[25] The results of this study for Herbal Preparation 1 were in accordance with the findings from a study by Dubey and colleagues^[26]. They reported significant improvements in total protein, serum albumin, blood volume, and LFTs, after six weeks of treatment with Herbal Preparation 1 as compared with placebo in patients with alcoholic cirrhosis (n=20)^[26]. On other hand, a multicenter trial in 200 patients with alcoholic cirrhosis treated with 450 mg of Herbal Preparation 2, daily did not confirm any benefit^[29]. A Cochrane systematic review of 13 randomized controlled trials also stated that Herbal Preparation 2 does not offer much benefit in ALD^[30].

Kolasani *et al* studied the prescription patterns of several drugs in patients with ALD and found that hepatoprotective agents, vitamins and minerals were the most prescribed drugs, followed by anti-ulcer drugs, antimicrobials, and others.^[36] Among hepatoprotective agents, Herbal Preparation 1 (36.9%) and UDCA (36.6%) were the most prescribed, followed by metadoxine (12.7%), pentoxifylline (9.0%), and Herbal Preparation 2 (4.9%)^[36]. The findings of this study were in consonance with the observations of the present study among the total screened patients (n=298).

The AEs reported in the current study were recorded in only a few patients. These AEs included gastrointestinal complaints, headache, back pain, dizziness, and dryness of the mouth. These adverse effects may not be associated with the current pharmacotherapies, as the patients also received concomitant medications during the treatment period. Some of these patients had complaints (such as nausea, indigestion) at the baseline, which might be attributed to the disease itself. The concomitant medications used by the patients like rifaximin, pantoprazole, propranolol, and glimepiride, are known to cause nausea, headache, dizziness, diarrhea and backpain; while headache, abdominal pain, dizziness, and loss of appetite are reported to be frequently associated with the use of aceclofenac.^[37-41] Further follow-up is required to determine any causal relationship of the current pharmacotherapies with the reported AEs.

The other drugs majorly used in the treatment of ALD also have reported gastrointestinal AEs. The most common reported AEs of pentoxifylline include nausea, vomiting, gastrointestinal issues (like abdominal discomfort, bloating, diarrhea), dizziness, headache, flushing, and others (chest pain, arrhythmias, and hypotension occur infrequently) [42]. Herbal Preparation 2 is usually reported to be associated with adverse events like gastrointestinal problems (e.g., nausea, diarrhea, dyspepsia, flatulence, abdominal bloating, abdominal fullness or pain, anorexia), headache, skin rashes, arthralgia, rhinoconjunctivitis, and anaphylaxis[43]. The findings of the study state that UDCA is more efficacious in improving the biochemical parameters in ALD patients, and thus, may delay progression to severe ASH and hepatitis.

Limitations of the study

In the present study, the patients were solely responsible for adhering to the treatment with no oversight. This might have contributed to lower compliance which may have led to the low observed therapeutic effect. The complete follow-up data for other pharmacotherapies was missing in this study to for effective comparison.

Conclusions

The present study demonstrates that UDCA and Herbal Preparation 1 were majorly used in the management of ALD. UDCA as a hepatoprotective agent has shown faster improvement in the liver biochemistry of ALD patients as compared to Herbal Preparation 1 in the first 4 weeks. Both the drugs were observed to be well tolerated by the patients. The study findings emphasize the early use of UDCA in ALD may help delay the progression of disease.

Ethical Approval: Independent Ethics Committee approval was taken

Conflict of Interest: Nil

Financial Disclosure: None

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