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Original Research Article

A prospective, multicentre, observational study of patients with chronic cholestatic liver diseases receiving Udiliv® in India: Splendid study

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ABSTRACT

Background: Data on clinical spectrum and etiology of chronic cholestatic liver disease (CCLD) in Indian patients is limited. This prospective, observational real-world study aimed to profile patients with CCLD being recommended Udiliv®, determine reasons for recommendation along with its safety and effectiveness.
Methods: CCLD patients (18-65 years) scheduled to receive Udiliv® as part of routine clinical practice were enrolled. Healthcare utilizations, clinical manifestations (jaundice, pruritus, fatigue) and liver biochemistry were assessed over 12 weeks. Reasons for recommending Udiliv® were recorded at the initiation of therapy.
Results: The intent-to-treat analysis population included 248 patients. The mean (±SD) age was 44.1(11.8) years and 78.23% were males. Majority (89.1%) were classified as intrahepatic cholestasis (IHC). Most common etiologies of IHC were alcoholic liver disease (ALD) (39.92%) and viral hepatitis (24.60%) followed by non-alcoholic fatty liver disease (NAFLD) (22.18%), which is less well known. Udiliv®, 300 mg twice daily was preferred dose due to known efficacy (73.39%), as standard of care (62.5%) and good tolerability (45.56%). There was reduction in healthcare visits, inpatient hospitalization and days off work, within 4 weeks of treatment initiation ($P<0.0001$). There was improvement in clinical presentation ($P<0.0001$) and reduction in biochemical markers over 12 weeks. The treatment was well-tolerated.
Conclusions: NAFLD, a less perceived etiology for CCLD, was found to be a significant contributor to CCLD. Physicians recommend Udiliv® due to its known efficacy and tolerability. Udiliv® reduced CCLD disease burden and was found to be an effective and well-tolerated treatment option.

Keywords: Alcoholic liver disease, Cholestasis, Non-alcoholic fatty liver disease, Ursodeoxycholic acid

INTRODUCTION

Cholestatic liver disease is a condition that results from an impairment of bile formation or reduction in bile flow due to obstruction. The clinical and biochemical characteristics of cholestatic disease are attributed to accumulation of toxic substances normally excreted in bile - in the liver, blood and other tissues.[1,2] Cholestasis also results in malabsorption of fat and fat-soluble vitamins due to inadequate postprandial bile acid concentrations in the upper small intestine.[1,2] Cholestasis is classified as acute or chronic, and based on the localization of the interference of bile flow or formation, extrahepatic and intrahepatic cholestasis.[3] The two major types of chronic cholestatic liver disease (CCLD) include primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC), followed by biliary atresia, hereditary cholestasis, intrahepatic cholestasis (IHC) of pregnancy,

gallstone disease and polycystic liver disease.[1] Both PBC and PSC are slowly progressive disorders, coursing over almost 1–2 decades from early to end-stage liver disease.[4] Population-based epidemiological studies have reported that the incidence and prevalence rates of both PBC and PSC vary (both by geography and age group) and seems to be increasing with time. Cholestasis of varying severity has also been found to be present in patients with viral hepatitis (Hepatitis A, B and E) and could be considered an indicator of disease progression.[5] Furthermore, in patients of alcoholic liver disease, alcohol- induced compression of intrahepatic biliary radicles and increased permeability of the bile ductules appears to predispose patients to develop cholestasis.[6]

Drug-induced cholestatic liver disease is a subtype of liver injury secondary to the administration of a hepatotoxic agent, characterized by abnormal liver function test values including alkaline phosphatase (ALP) and bilirubin levels.[7] Clinically, CCLD patients present with pruritus (itching), fatigue and jaundice (reflected by elevated serum bilirubin levels). In early stages, patients are usually asymptomatic and only biochemical disturbances such as elevated ALP and/or γ-glutamyl transpeptidase levels indicate cholestasis. Pruritus contributes to a large symptomatic burden to those suffering from CCLD; it is generalised, chronic, intermittent, and of varying severity. In a study, pruritus was reported by 69% of PBC patients, and for 75% of them, pruritus preceded the diagnosis of PBC.[8] Pruritus thus remains bothersome and very debilitating in patients of chronic cholestatic liver diseases with reported impaired sleep quality and quality of life.[9] Fatigue can be the most prevalent presenting symptom in 65% to 85% of cholestatic patients and can also have a significant impact on the patients' quality of life.[10] A recent retrospective survey in United States of America (USA) found that chronic liver disease is associated with a significant increase in medical costs and healthcare resource utilization over time.[11] Pharmacotherapy for cholestasis includes symptomatic treatment of pruritus along with management of complications such as osteopenia and fat-soluble vitamin deficiencies.[1]

Udiliv® tablets marketed in India by Abbott India Ltd contain ursodeoxycholic acid (150 mg, 300 mg and 600 mg). Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid with membrane-stabilizing, cytoprotective and immunomodulatory effects on liver cells.[2] It has been shown to exert beneficial effects in various liver diseases, especially those with cholestatic features. Replacement of endogenous bile acids by non-toxic bile acid such as UDCA protects the liver from accumulated toxic bile acids and retards the progression of these disorders. It prolongs survival in primary biliary cirrhosis and improves biochemical parameters of cholestasis in other underlying etiologies of chronic cholestasis including PSC, IHC of pregnancy, cystic fibrosis and total parenteral nutrition- induced cholestasis. There is also encouraging evidence supporting the use of UDCA in the treatment of alcoholic liver disease (ALD)[12], non-alcoholic fatty liver disease (NAFLD)[13], viral hepatitis[14], gall stones[15], and drug- or total parenteral nutrition (TPN)-induced cholestasis.[16]

It is believed that the profile of CCLD in India is different from the West with respect to etio-pathogenesis and clinical presentation. However, there is dearth of Indian data on underlying etiologies, clinical and biochemical profiling of patients presenting with CCLD. Furthermore, information on effectiveness of UDCA in the treatment of Indian patients with CCLD in terms of improvement of hepatic function profile as well as tolerability and compliance to therapy is inadequate. There is also a lack of data to characterize patient population with CCLD to whom UDCA is routinely recommended in the Indian clinical setting, along with limited understanding of the physicians' decision making process while initiating UDCA therapy. Observational studies collect information on the associated risk factors for the disease under study, thereby potentially improving the curative and preventive measures.[17] Observational studies are thus robust tools to evaluate the effectiveness and safety in non-controlled real-world settings.[17]

This study is the first of its kind real-world observational study in Indian patients with CCLD. The safety and efficacy of UDCA has been long established for more than two decades, primarily for the treatment of PBC. The primary objectives of this observational study were to determine the profile of CCLD patients treated with Udiliv® in the routine clinical care setting, and to gain critical insights into the decision making process of physicians recommending Udiliv® therapy in CCLD. The secondary objective of this study was to better understand the data on effectiveness, tolerability, and compliance of Udiliv® in the study population.

METHODS

Study site details

This prospective, multicentre, observational, single-arm study was conducted at 19 sites across 10 cities in India in compliance with International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guidelines. All study documents including protocol, subject information and patient authorization form were approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for each study site prior to the study conduct.

Patient inclusion and exclusion criteria

Indian patients aged between 18 and 65 years, attending the tertiary care hospitals and Gastroenterology outpatient clinics at designated study centres, diagnosed with CCLD and recommended Udiliv® were included in this study. Physicians recommended Udiliv® for the indication of CCLD according to the approved package insert of

Udiliv®. All patients provided written authorization to the investigator for use and disclosure of personal and health data prior to enrolment in the study. The study was conducted in accordance with the protocol, applicable local regulatory guidelines and ethical principles that have their origin in the Declaration of Helsinki. Individuals were excluded if they had hepatocellular or metastatic liver carcinoma; severe liver disease including but not limited to ascites, hepatic encephalopathy, hypoalbuminemia, or coagulopathy, Child-Pugh C liver disease; or had history of concomitant use of hepatotoxic drugs. Pregnant and lactating women were also excluded. Being an observational study, recommendation of Udiliv® therapy by the study physician preceded the decision of screening the patients for the study.

Udiliv® was recommended at different doses (150 mg, 300 mg, 600 mg, 900 mg or 1200 mg) initially for 8 weeks; however, the treatment was continued for approximately 12 weeks. The study intended to follow up patients every 4 weeks after enrolment (Visit 1, Day 0): Day 28 (Visit 2), Day 56 (Visit 3) and Day 84 (end of therapy [EOT], Visit 4). Study related information was recorded in the case report forms. Data collected at baseline included demography, lifestyle parameters (smoking status, tobacco chewing habit and alcohol consumption), medical history, clinical presentation, healthcare resource utilization (number of visits to health care service, number of days in hospital in last 4 weeks), work load effect (number of days off work in last 4 weeks), reasons for recommending Udiliv®, available laboratory results and Child-Pugh classification. No additional diagnostic or monitoring procedures (other than standard of care) were performed during the study conduct.

Study variables

The primary study variables included the clinical profile (demography, classification/underlying etiology) of cholestasis, burden of the disease in terms of healthcare resource utilization, workload effect (measured at all visits), and understanding the reason(s) for recommending Udiliv® (at baseline visit only). These primary study variables were captured based on information provided by the patient to the study physician, during the study visits.The secondary study variables included changes from baseline to EOT in laboratory parameters (serum total bilirubin [STB], serum conjugated bilirubin [SCB], serum alkaline phosphatase [ALP], serum gamma-glutamyl transferase [GGT], serum alanine transaminase [ALT] and serum aspartate transaminase [AST]), and clinical presentation of cholestasis (including jaundice, pruritus, fatigue, malaise etc). The tolerability and compliance to Udiliv® therapy were also evaluated. Compliance to Udiliv® during therapy was captured based on information provided by the patient to the study physician during the study visits. The intent-to-treat (ITT) population included patients who satisfied the eligibility criteria and received at least one dose during the study period. The per-protocol (PP) set included all enrolled patients who completed the study.

Statistical methods

As this was a non-randomized and non-comparative observational study with a primary objective to profile specific patient population with CCLD, formal sample size calculation was not performed. A total of 250 adult patients diagnosed with CCLD scheduled to receive treatment with Udiliv® were planned to be included in this study.

Standard descriptive analyses were performed to summarize study parameters. All values are expressed as mean±standard deviation (SD) or as counts and percentages. Continuous data (e.g. age) were summarized with the number of non-missing observations by descriptive statistics, i.e. mean ± SD, median, and minimum and maximum values. Categorical data (e.g. gender, race) were summarized using frequencies and percentages. For comparison of categorical data, Mann–Whitney *U* test was used. Pre- and post-baseline laboratory values, healthcare utilization, workload effect, symptoms and signs were summarized by visits and descriptive statistics has been presented. The number of patients with missing information was also summarized. Correlations were explored either using Pearson or Spearman correlation coefficients. Statistical significance was established as $P<0.05$.

RESULTS

A total of 249 patients were screened at 19 sites (tertiary care hospitals and Gastroenterology outpatient clinics) across 10 cities (Chennai, New Delhi, Lucknow, Coimbatore, Guwahati, Chandigarh, Kolkata, Jaipur, Trivandrum and Pune), for eligibility criteria of the study. Of the 249 patients screened, 248 patients meeting the eligibility criteria were enrolled (ITT population). Of these 248 patients, 27 patients discontinued the study, of which 15 were lost to follow up, 5 withdrew consent, and 7 discontinued due to other reasons (Figure 1). The remaining 221 patients were included in the PP analysis. The first patient was enrolled in July 2013 and the last patient final visit took place in June 2014.

Efficacy analysis of the ITT population is presented in this paper. The PP population showed a trend similar to the ITT population. The mean (±SD) age of the patients was 44.1 (11.8) years of which majority (n=194, 78.23%) were males. A total of 112 (45.16%) patients were alcohol consumers; 57 (6.12%) were smokers and 35 (31.25%) chewed tobacco. Amongst the 132 (53.23%) patients with at least one medical history, associated liver disorders reported in >3% of patients were chronic hepatitis B (n=24, 9.68%); jaundice (n=17, 6.85%) and chronic hepatitis C (n=9, 3.63%). The other co-morbid conditions (reported in >3%) were type II diabetes

mellitus (n=37, 14.92%), hypertension (n=32, 12.90%) and hypothyroidism (n=8, 3.23%).

Since this study was a post-marketing observational study, the physician was free to initiate any concomitant medications according to his or her own judgment. Hence, other hepatoprotectives recommended in this study population were silymarin (8.45%), pentoxifylline (6.05%), ademetionine (5.64%), vitamin E (4.83%), and L-Ornithine L-Aspartate (0.40%). Lactulose was another commonly used concomitant medication (8.44%) in this study population.

Table 1: Health care utilization.

Health care utilization	Statistics	Visit 1 (N=248)	Visit 2 (N=234)	Visit 3 (N=229)	Visit 4 (N=221)
Number of visits to healthcare service centers as outpatients within last 4 weeks because of CCLD	N	248	234	229	221
	Mean(±SD)	1.0 (1.9)	0.3 (0.6)	0.2 (0.6)	0.2 (0.6)
	Median	1.0	0.0	0.0	0.0
	Min-Max	0-17	0-4	0-5	0-3
	P-value*	-	<0.0001	0.2505	0.8439
Number of days in hospital in the last 4 weeks due to CCLD	N	248	234	229	221
	Mean(±SD)	0.8 (2.4)	0.3 (1.2)	0.1 (0.3)	0.0 (0.2)
	Median	0.0	0.0	0.0	0.0
	Min-Max	0-15	0-10	0-3	0-2
	P-value*	-	<0.0001	0.0232	0.2709

CCLD = chronic cholestatic liver disease; SD = Standard deviation; *P-values are based on comparison of post baseline visit with the previous visit using the Mann-Whitney U-Test.

Table 2: Days off from work (Baseline to EOT).

	Statistics	Visit 1 (N=248)	Visit 2 (N=234)	Visit 3 (N=229)	Visit 4 (N=221)
Days off work	Mean (± SD)	3.7 (4.6)	2.1 (5.2)	0.7 (2.3)	0.4 (1.1)
	Median	2.0	0.0	0.0	0.0
	Min-Max	0-28	0-47	0-28	0-7
	P value*	-	<0.0001	<0.0001	0.0108

EOT = end of therapy; SD = Standard deviation; *P-values are based on comparison of post baseline visit with the previous visit using the Mann-Whitney U-Test.

Table 3: Signs and symptoms of cholestasis (Baseline to EOT).

Signs and symptoms of cholestasis	Visit 1 (N=248) n (%)	Visit 2 (N=234) n (%)	Visit 3 (N=229) n (%)	Visit 4 (N=221) n (%)	P value*
Jaundice	179(72.18)	118(50.43)	72(31.44)	16(7.24)	<0.0001
Pruritus	110(44.35)	89(38.03)	25(10.92)	7(3.17)	<0.0001
Fatigue	160(64.52)	81(34.62)	6(20.09)	25(11.31)	<0.0001
Malaise	86(34.68)	26(11.11)	11(4.80)	6(2.71)	<0.0001

EOT = end of therapy; *P-values are based on comparison of Visit1 and Visit 4 values using Chi Square Test.
Note 1: Percentages are based on the number of patients for the particular visit; Note 2: At each level of summarization selection can be multiple.

Classification of cholestasis with underlying etiology

Classification: Majority of the patients were identified as having IHC (n=221; 89.1%) followed by two (0.81%) patients each with extrahepatic cholestasis (EHC) and drug-induced cholestasis, respectively. Few patients had an overlapping etiology of both IHC and EHC (n=12; 4.84%); IHC, EHC, and drug-induced cholestasis (n=10; 4.03%); and IHC and drug-induced cholestasis (n=1; 0.40%).

Etiologies: ALD was the most common etiology in patients with IHC (n=99; 39.92%) followed by viral hepatitis (n=61; 24.60%) and NAFLD, (n=55; 22.18%). PBC was reported in 18 (7.26%) patients, autoimmune hepatitis in 4 (1.61%) patients and only one patient

(0.4%) had PSC. Inflammatory processes (n=14; 5.65%), choledocholithiasis (n=10; 4.03%) and postsurgical alterations (n=3; 1.21%) were the etiological factors associated with EHC.

Antibiotics (n=6; 2.42%) and angiotensin-converting enzyme (ACE) inhibitors (n=5; 2.02%) were identified in the pathogenesis of drug-induced cholestasis (Figure 2).

Table 4: Laboratory parameters at different visits.

Parameter		Visit 1	Visit 2	Visit 3	Visit 4
AST (Units/L)	n	229	80	99	79
	Median (Min, Max)	86.0 (15,8500)	64.5 (15,211)	46.0 (16,477)	38.0 (1,640)
ALT (Units/L)	n	235	80	99	79
	Median (Min, Max)	71.3 (5,6817)	56.0 (14,402)	40.0 (15,573)	38.0 (17,720)
ALP (Units/L)	n	215	69	93	76
	Median (Min, Max)	198.0 (19,2307)	140.0 (38,1294)	138.0 (18,788)	133.0 (57,752)
GGT (Units/L)	n	88	37	49	33
	Median (Min, Max)	93.0 (5,1325)	93.0 (12,527)	67.0 (11,407)	54.0 (9,251)
STB (mg/dL)	n	240	82	100	79
	Median (Min, Max)	3.4 (0, 33)	1.3 (0, 15)	1.0 (0, 9)	0.9 (0, 12)
SCB (Units/L)	n	221	78	94	76
	Median (Min, Max)	1.6 (0, 26)	0.6 (0, 12)	0.5 (0, 5)	0.3 (0, 6)

ALP = Alkaline phosphatase; ALT = Alanine transaminase; AST = Aspartate transaminase; GGT = Gamma-glutamyl transferase; SCB = Serum conjugated bilirubin; STB = Serum total bilirubin.

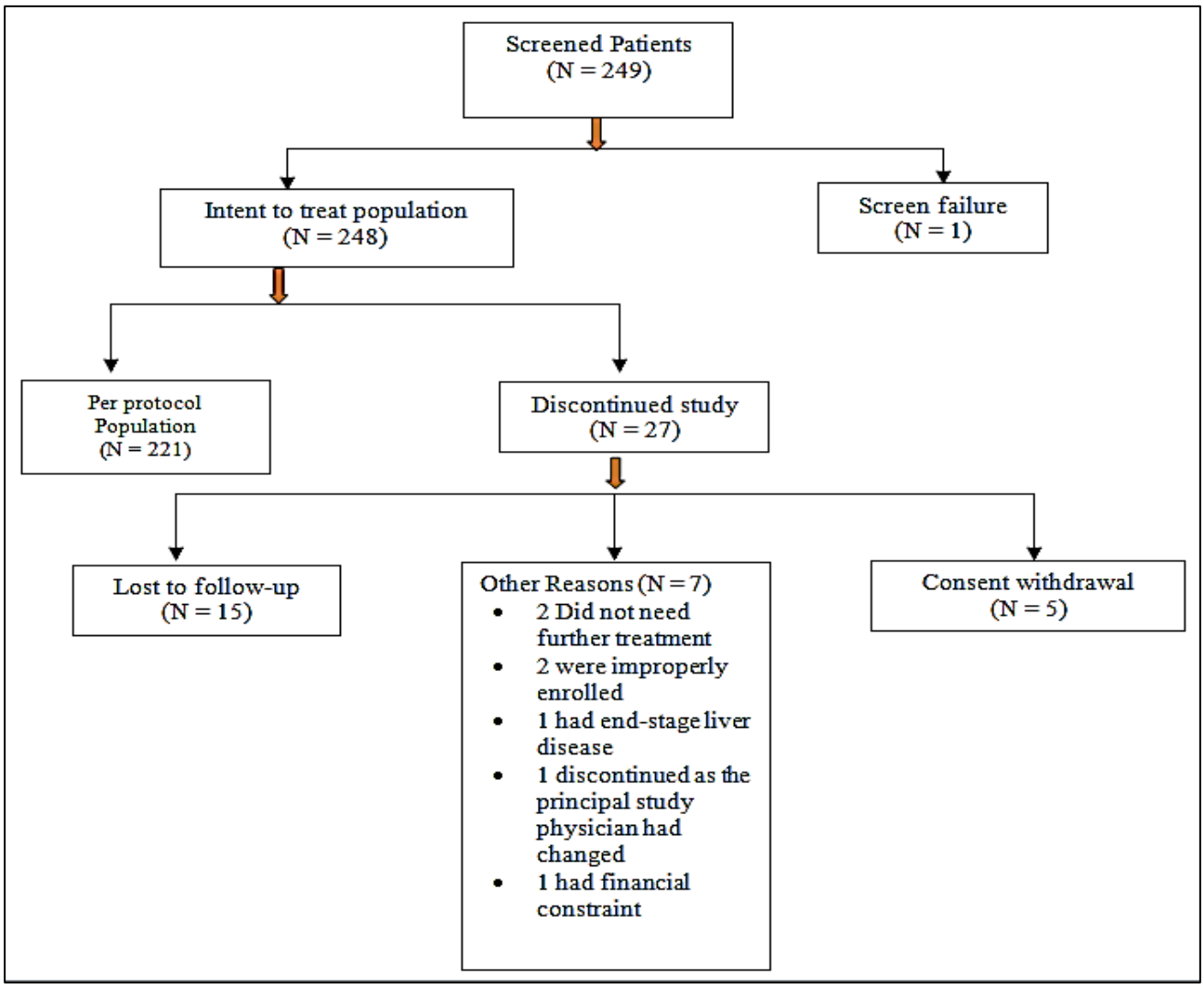
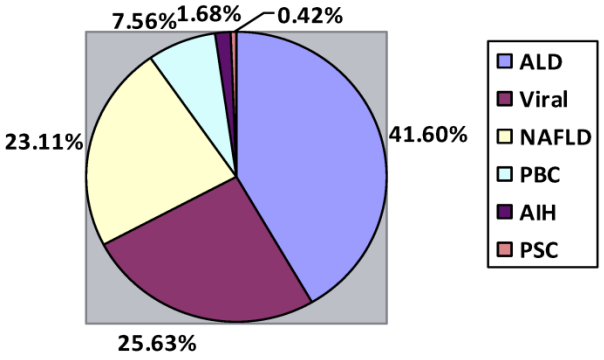


Figure 1: Patient disposition.

Burden of disease in terms of healthcare resource utilization

Healthcare visits: The mean number of visits to a healthcare service center in last 4 weeks at baseline visit was 1. Reduction in the mean (±SD) number of visits to a healthcare service center as an outpatient from baseline to Day 28 (1.0 [1.9] to 0.3 [0.6] visits) was statistically significant (P<0.0001). The number of visits reduced further to 0.2 (0.6) visits at Day 56 and EOT (Table 1).



ALD: Alcoholic liver disease, NAFLD: Non-alcoholic fatty liver disease, PBC: Primary biliary cirrhosis, AIH: Autoimmune hepatitis, PSC: Primary sclerosing cholangitis

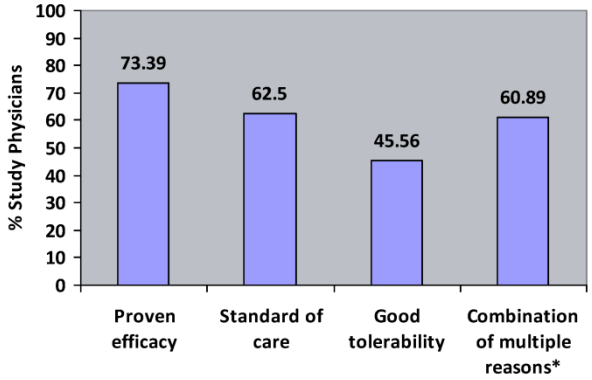
Figure 2: Etiologies of intrahepatic cholestasis.

Inpatient hospitalization: At baseline visit, mean number of inpatient hospitalizations in last 4 weeks was 0.8 days. Reduction in the mean (±SD) number of days in the hospital from baseline to Day 28 (0.8 [2.4] to 0.3 [1.2] days) was also statistically significant (P=0.0009). The number of inpatient hospitalizations reduced further to 0.3 (1.2) days at Day 56 and 0.0 (0.2) days at EOT (Table 1).

Days off work: The mean number of days off work in last 4 weeks at baseline was 3.7 days. The mean (SD) number of days off work reduced significantly from 3.7 (4.6) days at baseline to 2.1 (5. 2) days at Day 28 (P <0.0001), 0.7 (2.3) days at Day 56 (P<0.0001) and 0.4 (1.1) days at EOT (P=0.0108), indicating statistically significant and consistent improvement with time (Table 2).

Pharmacotherapy with Udiliv®

Among different doses of Udiliv®, 300 mg twice daily was the most commonly recommended dose; all patients continued the therapy for a period of 12 weeks. There were multiple and overlapping reasons for initiating treatment with Udiliv® in CCLD patients. The most prevalent reason cited by the physicians was its proven efficacy in CCLD (recommended to 182 patients; 73.39%). The other reasons mentioned were standard of care (n=155; 62.5%), good tolerability (n=113, 45.56%), and a combination of two or more reasons (efficacy, tolerability or standard of care) in approximately 151 patients (60.89%) (Figure 3).



CCLD: Chronic cholestatic liver disorders; * Combination of two or more reasons (efficacy, tolerability or standard of care).

Figure 3: Reasons for recommending Udiliv® in CCLD.

Clinical presentation (Baseline and EOT)

At baseline, patients presented with various signs and symptoms of cholestasis. The most frequently reported symptoms were jaundice (72.18%), fatigue (64.52%), pruritus (44.35%) and malaise (34.68%). The reductions in clinical presentation of cholestasis (jaundice, pruritus, fatigue, malaise) were statistically significant at EOT compared to baseline (P<0.0001) (Table 3).

Impact of pruritus on daily activities: There was clinically significant reduction in impact of pruritus on daily activities from baseline to EOT. Patients with severe impact shifted to moderate category and moderate impact shifted to mild during subsequent visits. A total of 6 and 24 patients with severe and moderate impact, respectively at baseline, had none in both categories at EOT; and 80 patients with mild impact at baseline had only 7 patients with same degree at EOT. The improvement shifts for impact of pruritus on daily activities were also reported during 4 weekly follow up visits: Day 28 (moderate to mild [6 patients; 18.0%] and severe to mild [4 patients; 4.5%]); Day 56 (moderate to mild [4 patients; 16.0%]) and Day 84 (moderate to mild [1 patient; 14.3%).

Severity of pruritus: The severity of itching also changed from severe to moderate and moderate to mild during subsequent visits, leading to increased proportion of patients in the mild and moderate categories at EOT. There was statistically significant decrease in the number of patients having mild itching severity from baseline to EOT (81 patients [32.66%] to 7 patients [2.82%] respectively; P<0.0001)). The improvement shifts in the severity rate of itching were reported across visits as follows: Day 28 (moderate to mild [17 patients; 19.1%] and severe to mild [4 patients; 4.5%]); Day 56 (moderate

to mild [5 patients; 20.0%]) and Day 84 (moderate to mild [2 patients; 28.6%]).

Hours of itching: At Day 28 and Day 56, improvement shifts in hours of itching per day were reported in 12 patients (13.5%) and three patients (12%), respectively, who shifted from an itching duration of 6 to 11 hours to less than 6 hours. Also, four patients (4.5%) shifted from an itching duration of more than 12 hours to less than 6 hours at Day 28. At Day 28, a total of 68 (76.4%) patients reported improvement from 'Is still the same' to 'Better but still present', while 2 patients reported improvement from 'Worsened' to 'Better but still present'. At Day 56, 16 (64%) patients reported improvement from 'Is still the same' to 'Better but still present' and 2 (8%) reported 'Better but still present' from 'Worsened'. 'Better but still present' to 'resolved completely' was reported by 2 patients (28.6%) at EOT.

Among the 78 (31.45%) patients with available Child-Pugh scores at baseline, the Child-Pugh classification was A in 22 (8.87%) patients and B in 56 (22.58%). Due to unavailability of laboratory data in these patients at EOT, Child-Pugh scoring could be calculated in 40 patients only (22 [8.87%] still had Child-Pugh A and 18 [7.26%] had Child-Pugh B). None of the patients had a Child-Pugh C liver disease.

Laboratory evaluation

At baseline, serum laboratory results were available for a majority of the liver function parameters except for GGT (88, 35.34%). Although these tests are recommended routinely at all visits as part of standard of care, the test results were not available for a large number of patients across the visits. As per the available data, the median values of ALT, AST, STB, SCB, GGT and ALP decreased by 46.7%, 55.8%, 73.5%, 81.3%, 41.9% and 32.8%, respectively, from baseline to EOT (Table 4).

On Day 28, the reported compliance with Udiliv® treatment was 100%. Treatment compliance with Udiliv® continued to be 100% on Day 56, while it was 99.10% at EOT.

Safety

Udiliv® was well tolerated during the 12 weeks of therapy and no treatment discontinuation occurred. No adverse drug reactions (ADRs) were reported during the entire course of treatment.

DISCUSSION

The present study, the first of its kind, was conducted in a representative population of Indian patients presenting with CCLD. This post-marketing observational study was designed to profile Indian CCLD patients into etiological classification of IHC, EHC, drug-induced cholestasis or a combined category, with overlapping etiologies. Other important objectives of this study were to gain insights into the decision making process of physicians while recommending Udiliv® and to evaluate effectiveness, safety/tolerability and compliance of Udiliv® therapy in routine clinical practice in India. Such real-world, observational studies serve to assess the burden of disease etiologies, healthcare resource utilization, and overall impact on health-related quality of life. Additionally they can identify changes, if any, in the prescription patterns of the drug under consideration and reasons thereof.

A majority of this study population had IHC (89.1%); a well-known categorization of CCLD worldwide.[3] Literature from the Western world reports a majority of the adult patients with CCLD having either PBC or PSC. The prevalence of PBC is between 1.9 and 40.2 per 100,000 inhabitants, whereas the prevalence of PSC is 16.2 per 100,000 inhabitants.[18] In contrast, PBC as the etiological factor for IHC was reported in about 7.26% and PSC in less than 1% of the patients in this study. This represents a distinct etiological profile of CCLD in the Indian population as compared to the West. In this study, secondary causes of IHC dominated the etiologies of chronic IHC, being reported by almost 85% of the patients (ALD: 39.92%; viral hepatitis: 24.6% and NAFLD: 22.18%). Alcoholic liver disease was found to be the major etiology underlying IHC in more than one-third patients. Although the pathophysiology of cholestasis in ALD is not that well established, alcohol-induced cholestasis is mediated by compression of intrahepatic biliary radicles and increased permeability of the bile ductules.[6] Moreover, alcoholism leading to ALD is one of the primary causes of liver diseases in India.[19] A significant finding of the present study was the presence of NAFLD in a considerable number of CCLD patients (about one-fifth) as an underlying etiology of IHC. This highlights the growing disease burden of NAFLD in Indian population and represents an effect of increasing urbanization, high fat intake and sedentary lifestyles.[20] A cholestatic variant of NAFLD has been described in a retrospective case-control study of 20 obese patients with elevated aminotransferase levels and negative serological markers for other liver diseases. Also, NAFLD patients with biochemical cholestasis have more advanced histological impairment than non-cholestatic patients matched for age, sex and body mass index.[21] These data highlights the importance of screening for NAFLD in Indian patients presenting with cholestasis, in addition to the more commonly known etiologies of IHC.

CCLD is regarded as a model disease for UDCA therapy; studies in patients with PBC, PSC and IHC of pregnancy have demonstrated marked improvements in serum liver chemistries when the therapy was used for longer duration.[22] In this study, the primary reason for physicians to recommend Udiliv® was its efficacy in CCLD (73.39%). Udiliv® was also recommended as a standard of care for CCLD patients by a significant number (62.5%) of study physicians, along with good tolerability by 45.46% study physicians. These data

represents a high acceptance and belief in UDCA amongst Indian physicians treating CCLD.

Udiliv® treatment for 12 weeks significantly reduced the number of visits to the healthcare centres as outpatients, days in the hospital and number of days off work compared to baseline (P<0.0001, P=0.0009, P<0.0001 respectively). This reduction may be directly linked to improvements in various assessments including signs and symptoms of cholestasis, especially pruritus and biochemical parameters. These, in turn may have a direct impact on patient's daily activities and overall QoL.

Pruritus is known to be a debilitating symptom in CCLD with varying severity. If nocturnal, it disrupts sleep and adversely affects the patient's QoL. It can be a deterrent to daily activities and personal relationships, and may lead to depression and even suicidal intent in extreme cases.[23] UDCA is one of the most commonly recommended treatments for relief of pruritus in patients with cholestasis. Patients in our study cohort reported marked improvement in pruritus in terms of severity, hours of itching per day and impact on daily activities. Another important response to Udiliv® treatment was significant improvement in fatigue, which is known to be associated with a favorable outcome in patients with CCLD.[22]

Even though laboratory assessment data were available only for approximately one-third of the patients, there was a significant decrease in the elevated liver function parameters at EOT as compared from baseline. Udiliv® therapy showed high compliance rate owing to good tolerability and no safety issues, thereby augmenting its effectiveness parameters. Good tolerability of Udiliv® improving treatment adherence was also cited as one of the important factors responsible for physician preference to Udiliv® therapy in CCLD patients.

As this is the first study conducted in Indian patients of CCLD, more such studies with large sample size across multiple tertiary centres in India, with long term evaluation of the profile of such patients is recommended to validate the findings of this study.

In conclusion, this study revealed the unique clinical profile of CCLD patients with secondary etiologies of IHC being prevalent in Indians including ALD, viral hepatitis and NAFLD. NAFLD, though perceived as not commonly associated with CCLD contributes significantly as an etiology of CCLD in Indian patients, in this study. Physicians prefer Udiliv® therapy in CCLD because of its known efficacy and good tolerability, and thereby consider UDCA to be the standard of care in patients of CCLD. This study also demonstrated that Udiliv® decreases healthcare resource utilization owing to its beneficial effects on clinical and biochemical parameters. Udiliv® is safe and well tolerated with a very high compliance rate. Considering the projected increase in the burden of CCLD in India, especially due to rising prevalence of NAFLD, Udiliv® offers an effective and well tolerated treatment option which could help mitigate this disease burden significantly.

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