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Heptral® (Ademetionine) in patients with chronic alcoholic liver disease: Results of a multicentre observational study in Indian patients

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Abstract: Aim: This observational study was aimed at assessing the effectiveness and tolerability of Heptral® (brand of ademetionine 1, 4-butane disulfonate) in Indian patients presenting with intrahepatic cholestasis (IHC) due to chronic alcoholic liver disease (ALD). The study also aimed at understanding the prescribing practice of physicians as well as the profile of patients being prescribed Heptral®. **Material and Methods:** This prospective observational study included 250 patients across 21 study sites. The assessments of health-economic parameters, liver biochemistry, signs and symptoms of IHC (fatigue, jaundice and pruritus) were performed at two visits, ie, at baseline and after six weeks of Ademetionine treatment. Ademetionine was prescribed as part of the routine medical treatment as per the local label and not as a study intervention. **Results:** Of the 243 patients included in the analysis population, cirrhosis was present in 42.8% (104); 72% (175) were heavy drinkers, ie, taking four or more drinks per day. Ademetionine administration resulted in significant ($p<0.0001$) reduction in health-economic burden (number of days off work [-4.28 days], number of visits to healthcare services as an outpatient [-0.72], number of days in hospital [-1.42 days]), levels of biochemical markers, signs and symptoms of IHC. Beneficial effects were seen irrespective of presence/absence of cirrhosis, drinking patterns (heavy or not heavy drinkers), varied dosage of Heptral® and use of concomitant medications. **Conclusions:** Administration of Heptral® in patients with ALD and IHC resulted in significant improvement in burden of disease, laboratory markers, signs and symptoms of cholestasis. The treatment was well tolerated.

Key words: alkaline phosphatase, bilirubin, cirrhosis, fatigue, health-economic parameters, jaundice, pruritus, S-adenosyl-L-methionine, SAMe, serum γ-glutamyl transpeptidase

Introduction

S-Adenosyl-L-methionine (SAMe, also known as ademetionine) is a metabolite that plays a pivotal role in multiple cellular pathways. It acts as a methyl donor for multitude of biological methylation reactions (transmethylation) and participates in the synthesis of glutathione (transsulfuration). Glutathione (GSH) is a major endogenous

antioxidant that protects cells against injury by scavenging free radicals involved in the pathogenesis of alcoholic liver disease (ALD). Chronic deficiency of ademetionine due to its altered synthesis is associated with cholestasis in hepatitis and cirrhosis. Detailed understanding of these biochemical pathways has been highlighted in several reviews [1-3]. Prevention of ademetionine deficiency was confirmed beneficial in intrahepatic cholestatic states in controlled clinical studies [4-7]. IHC is clinically characterized by symptoms such as pruritus and jaundice, and elevation of levels of serum total bilirubin (STB), serum conjugated bilirubin (SCB), serum alkaline phosphatase (ALP), and serum γ-glutamyl transpeptidase (γGT). Parenteral as well as oral administration of ademetionine improved both the biochemical markers and subjective symptoms indicative of IHC [6,7]. However, there is lack of data to understand the use of ademetionine in well characterized disease specific patient populations. This observational study was conducted to understand the effectiveness and tolerability of Heptral® (brand of ademetionine 1, 4-butane disulfonate) in the Indian patient population with intrahepatic cholestasis in chronic liver disease due to ALD, under real life settings. The primary objective of the study was to understand the effect of Ademetionine treatment on health-economic parameters associated with the disease. The study also intended to understand the physician's decision-making process and characterize the patient population for presence/absence of cirrhosis, drinking patterns (heavy or not heavy drinkers), dosage of Heptral® and the use of concomitant medications.

Ademetionine-1,4-butanedisulphonate is approved for the management of IHC and liver diseases and is being marketed in India since September 2010.

Materials and Methods

This was a prospective, multicentre, observational study of six weeks treatment duration, to monitor the effectiveness and safety of ademetionine in patients with intrahepatic cholestasis in chronic liver disease due to ALD. The study was conducted over a period of approximately 11 months (September 2011 to August 2012) across 21 study sites in India.

Approvals from central and local ethics committees were obtained for all study sites, except for one site for which only local ethics committee approval was obtained prior to enrollment of first patient in the study. All subjects provided written authorization to the investigator for use and disclosure of personal and health data prior to enrollment 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.

No treatment was administered as part of the study intervention. Decision to prescribe Ademetionine was not influenced by subject's participation in the study. Oral Ademetionine (up to 1600 mg/day) was prescribed as a part of the routine medical treatment by the physician, as per the local label. The physician could initiate any co-prescription as per his/her clinical judgment.

Patients

The study included adults (18-65 years) of either sex, with chronic ALD complicated by IHC as diagnosed by the physician, who were prescribed Ademetionine according to the local label and who provided written authorization to the investigator. Patients with any contraindications to the administration of Ademetionine were excluded. Patients with hepatocellular or metastatic liver carcinoma; severe liver disease such as ascites, hepatic encephalopathy, hypoalbuminemia, coagulopathy; those receiving any hepatotoxic medication; any other condition due to which investigator judged the participation was not possible, were excluded. Pregnant or lactating women were excluded from the study. Patients previously enrolled in this study were also excluded.
The study included two site visits by the patients. The first one was baseline visit (V1) at which Ademetionine was initiated and the second visit (V2) was at treatment completion (42 days after the first dose of ademetionine). First administration of Ademetionine could be within three days of the baseline visit. These visits were scheduled as a part of routine practice by the physician.

Study assessments

At baseline visit (V1), the patients signed the authorization form and were assessed for inclusion and exclusion criteria. At this visit Ademetionine was prescribed to the patient and the demographics with medical history of the patient were recorded. Assessment of health-economic parameters, liver biochemistry, signs and symptoms of IHC (fatigue, jaundice and pruritus) was done at the baseline visit and the second visit which was scheduled at the

completion of Ademetionine treatment, i.e., after 42 days. Health-economic parameters included number of days off work, number of visits to healthcare services as an outpatient and number of days spent in the hospital due to liver disease in the preceding six weeks. Laboratory tests for liver biochemistry included serum total bilirubin (STB), serum conjugated bilirubin (SCB), serum alkaline phosphatase (ALP), serum alanine transaminase (ALT), serum aspartate transaminase (AST), and γ-glutamyl transpeptidase (γGT).

Patients were monitored for serious adverse events (SAEs) throughout the study and a telephonic contact was made with all patients after 30 days of the second visit (72 days after the first visit) to record any occurrence of SAE.

Even though observational studies with a single cohort generally allow limited conclusions for lack of a comparator, such conclusions are more valid in chronic diseases such as chronic ALD.

Statistical considerations

Descriptive statistics for continuous data included mean ± standard deviation (SD), and the range (minimum, maximum). For categorical data, frequency distribution and percentages were calculated. Statistical test such as Wilcoxon signed rank sum test, McNemar's test as appropriate were used to analyze change from baseline value. A *p*-value of <0.05 was considered as statistically significant. Subgroup analysis was performed based on patients with (i) presence/absence of cirrhosis, (ii) varied dosage of Ademetionine (less than 800 mg or 800-1600 mg per day), (iii) amount of alcohol consumption (heavy/not heavy drinkers) and (iv) use of concomitant medications (with/without). Adverse events were presented using Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs). Statistical analysis was performed using SAS version 9.2.

Results

Baseline demographic and clinical characteristics

A total of 250 patients were enrolled in this study and comprised the full analysis set. Seven (2.8%) patients classified as having Child-Pugh class C were excluded from the analysis; therefore results for effectiveness were based on data from 243 patients constituting the modified Intention-To-Treat (mITT) population. The baseline demographic and clinical characteristics of these patients are summarized in Table 1 and Table 2, respectively. The mean age was 43.97 ± 9.38 years and 99.6% (242/243) patients were males.

Among 243 patients in the evaluable population, cirrhosis was present in 42.8% (104) while 57.2% (139) did not have cirrhosis. Furthermore, 14.8% (36) and 6.2% (15) patients were classified as Child-Pugh class A and B respectively. Approximately 72% (175) were classified as heavy drinkers, i.e., taking four or more drinks in a day.

Table 1: Baseline Demographic Characteristics

Demographic Characteristics		mITT (N = 243)
Gender (n [%])	Male	242 (99.6%)
	Female	1 (0.4%)
Age (mean ± SD) (years)		43.97 ± 9.38
Race (n [%])	Asian	243 (100.0%)

Abbreviation: mITT = modified Intent-To-Treat

A much higher proportion (90.5% [220]) of the patients were prescribed Ademetionine dose of 800-1600 mg/day compared to 9% (22) who were prescribed a dose of less than 800 mg/day. Concomitant medications were being taken by 91.4% (222) patients. The most common concomitant medications included ursodeoxycholic acid (bile acid preparation) used by 36.6% (89) patients; followed by pantoprazole, rabeprazole (proton pump inhibitors), and lactulose (laxative) used by 21.4% (52), 18.5% (45) and 12.3% (30) patients, respectively.

Table 2: Baseline Clinical Characteristics

Clinical Characteristics		mITT (N = 243)
Child-Pugh (n [%])*	A	36 (14.8%)
	B	15 (6.2%)
Cirrhosis (n [%])*	With cirrhosis	104 (42.8%)
	Without cirrhosis	139 (57.2%)
Drinking habits (n [%])	Heavy drinkers†	175 (72.0%)
	Not heavy drinkers	68 (27.9%)
Ademetionine Dose (mg/day) (n [%])‡	800-1600	220 (90.5%)
	<800	22 (9.0%)
Concomitant medications (n [%])	Yes	222 (91.4%)
	No	21 (8.6%)
Complications (n [%])*	Cholangitis	11 (4.5%)
	Other liver diseases	10 (4.1%)
	Non-liver diseases	25 (10.3%)

Abbreviation: mITT = modified Intent-To-Treat,

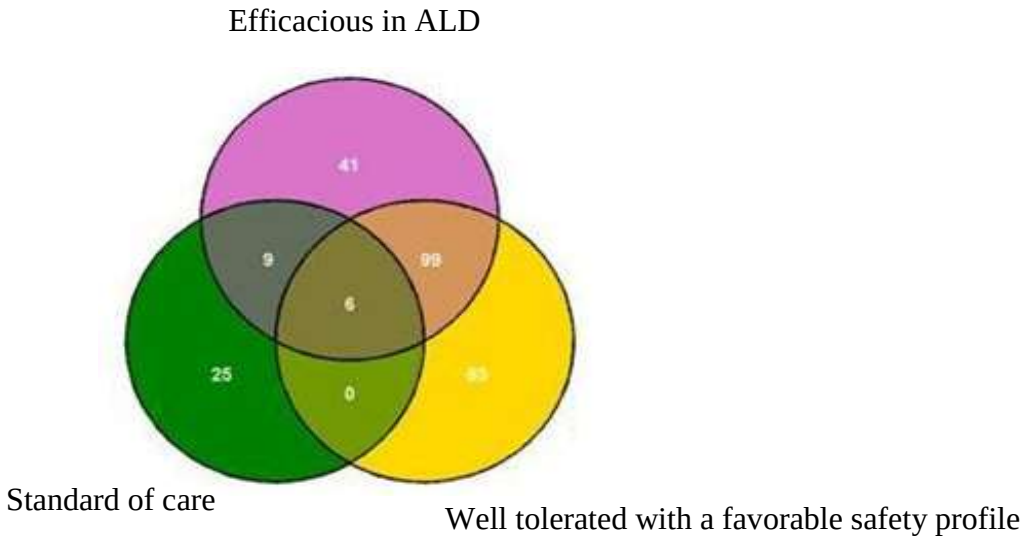
*n (%) stands for number (percentage) of patients with primary diagnosis

†Heavy drinkers were defined as those taking four or more drinks in a day

‡Data missing for one patient

Reason(s) stated by the physicians for prescribing Ademetionine to all 243 patients enrolled in the study were recorded (Figure 1). For 40.7% (99) patients, the physicians provided two reasons for prescribing Heptral®, these were 'efficacious in ALD' and 'well tolerated with a favorable safety profile'. For almost one-fourth (25.9% [63]) of the patients, the reason for prescribing Ademetionine was 'well tolerated with a favorable safety profile'. For 16.5% (40) and 10.3% (25) patients, the reasons provided by the physicians were 'efficacious in ALD' and 'standard of care', respectively.

Figure 1: Reasons provided by the physicians for prescribing Heptral®



Abbreviation: ALD = Alcoholic Liver Disease

Please note that numbers in the Venn diagram represent frequency

The mean daily dose during the study was 922.41 ± 264.45 mg, and mean duration of administration was 44.53 ± 9.14 days.

Total of four subjects discontinued prematurely, one was lost to follow-up and three due to SAEs. Details are provided under the *Safety assessment*s section.

Burden of disease

Analysis of the burden of disease was based on data collected from 235 patients at visit 1 and visit 2 (Figure 2, Table 3). At baseline, mean length of stay in hospital was 1.88 ± 3.67 days that decreased to 0.46 ± 2.01 days at visit 2. Mean number of visits to the doctor decreased from 1.87 ± 1.59 at baseline to 1.15 ± 1.06 at visit 2. Similarly, mean number of days off from work also decreased from 9.71 ± 12.36 days at baseline to 5.43 ± 9.86 days at visit 2. Reduction in all three parameters of burden of disease was observed across all subgroups (Table 3). Moreover, this reduction was statistically significant ($p<0.05$) in the following subgroups of patients: (i) with as well as without cirrhosis, (ii) receiving either less than 800 mg/day or 800-1600 mg/day of Heptral®, (iii) heavy drinkers, and (iv) those receiving concomitant medications. Patients classified as having Child-Pugh A or B also showed reduction in the burden of disease.

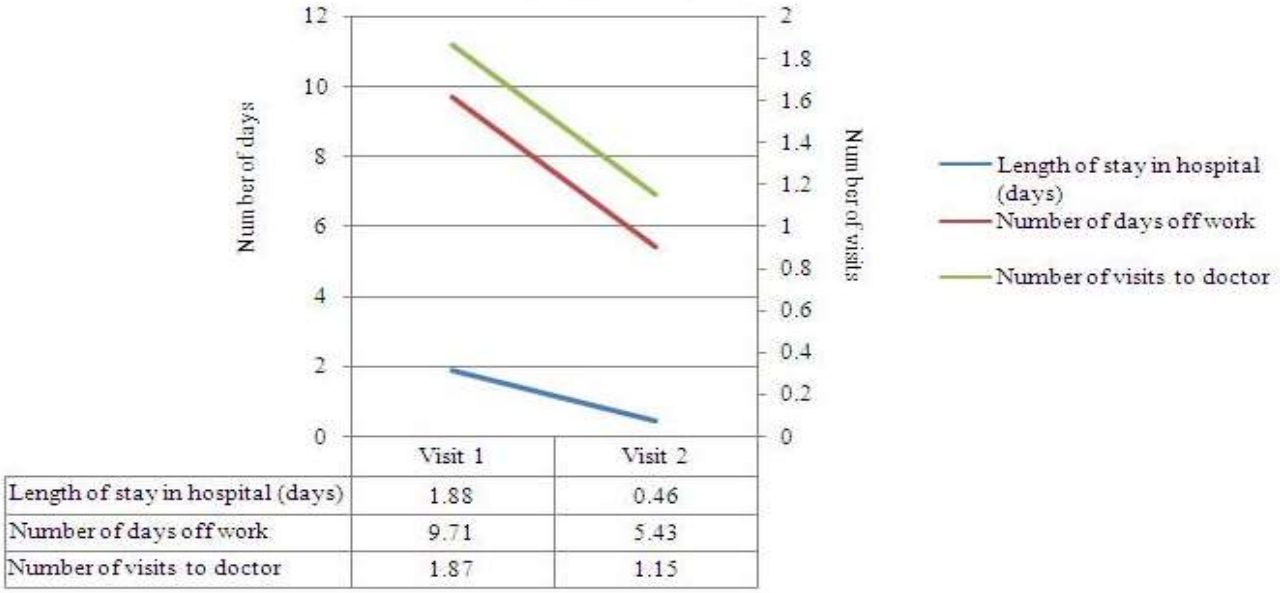
Table 3: Change in Health-Economic Parameters from Baseline (visit 1) to visit 2

	n*	Change in length of stay in hospital (days)		Change in number of visits to doctor		Change in number of days off from work	
		Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value
Overall†	235	-1.42 (3.68)	<0.0001	-0.72 (1.43)	<0.0001	-4.28 (9.67)	<0.0001
With cirrhosis†	99	-1.97 (4.95)	<0.0001	-0.99 (1.42)	<0.0001	-6.85 (11.12)	<0.0001
Without cirrhosis†	136	-1.01 (2.31)	<0.0001	-0.53 (1.41)	<0.0001	-2.41 (8.01)	<0.0001
Heavy drinkers‡	168	-1.65 (3.22)	<0.0001	-0.79 (1.35)	<0.0001	-4.83 (10.37)	<0.0001
Not heavy drinkers‡	67	-0.84 (4.63)	0.1050	-0.55 (1.62)	0.0018	-2.91 (7.55)	0.0003
Dose 800-1600 mg/day‡	213	-1.33 (3.74)	<0.0001	-0.68 (1.48)	<0.0001	-4.15 (9.74)	<0.0001

Dose <800 mg/day‡	22	-2.27 (2.96)	0.002	-1.14 (0.77)	<0.0001	-5.59 (9.08)	0.0044
With concomitant medication‡	215	-1.43 (3.72)	<0.0001	-0.75 (1.45)	<0.0001	-4.45 (10.04)	<0.0001
Without concomitant medication‡	20	-1.25 (3.27)	0.0938	-0.45 (1.19)	0.1348	-2.45 (3.63)	0.0088

Abbreviation: SD = Standard Deviation, *Only the patients with values at both baseline (visit 1) and visit 2 were considered for analysis, †p-value calculated by Wilcoxon signed rank test , ‡p-value calculated by Wilcoxon signed rank sum test

Figure 2: Change in Health-Economic Parameters from Baseline (visit 1) to visit 2 [N = 235].



	Visit 1	Visit 2
Length of stay in hospital (days)	1.88	0.46
Number of days off work	9.71	5.43
Number of visits to doctor	1.87	1.15

Laboratory parameters

Overall baseline and final values of the biochemical indicators are presented in Figure 3 and Table 4. Levels of biochemical indicators (STB, SCB, ALP, GGT, ALT and AST) post Ademetionine treatment were statistically lower ($p<0.0001$) compared to baseline values.

Laboratory parameters for subgroups are presented in Table 4. Subgroup analysis based on the presence or absence of cirrhosis showed that the decrease in levels of STB, SCB and AST was statistically significant ($p<0.05$) in both cirrhotic and non-cirrhotic patients; however decrease in the levels of ALP, γGT and ALT was statistically significant ($p<0.0001$) only in non-cirrhotic patients.

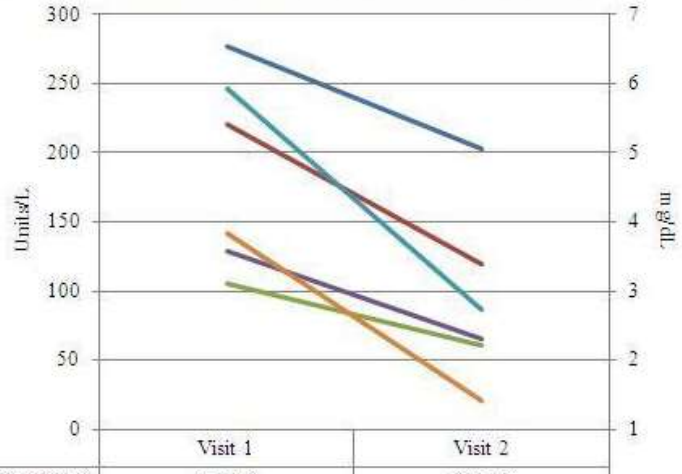
Decrease in STB, SCB, ALP, ALT and AST levels was statistically significant ($p<0.05$) irrespective of the dosage, i.e., less than 800 mg/day or 800-1600 mg/day. Decrease in γGT level was statistically significant ($p<0.0001$) only for patients who received the dose of 800-1600 mg/day. There was no patient who received a dose of less than 800 mg/day with γGT data available for both the visits.

In the subgroup analysis based on alcohol consumption it was seen that decrease in levels of all measured biochemical markers (STB, SCB, ALP, γGT, ALT and AST) was statistically significant ($p<0.05$) for heavy drinkers as well as for non-heavy drinkers.

Subgroup analysis based on the use of concomitant medications revealed a statistically significant ($p<0.0001$) decrease in all measured biochemical markers (STB, SCB, ALP, γGT, ALT and AST) in

these patients who received concomitant medications. Data for biochemical markers of only one patient without concomitant medication was available; therefore no statistical significance could be established.

Figure 3: Laboratory Parameters at baseline (visit1) and after treatment completion (visit 2) – Overall



	Visit 1	Visit 2
ALP (Units/L)	276.51	203.13
γGT (Units/L)	220.51	119.19
ALT (Units/L)	105.65	60.29
AST (Units/L)	128.83	64.78
STB (mg/dL)	5.91	2.72
SCB (mg/dL)	3.82	1.4

Abbreviations:
ALP = Serum Alkaline Phosphatase, ALT = Serum Alanine Transaminase, AST = Serum Aspartate Transaminase, γGT = Serum γ-Glutamyl Transpeptidase, SCB = Serum Conjugated Bilirubin, STB = Serum Total Bilirubin

p-values <0.0001 (for all three parameters, calculated by Wilcoxon signed rank sum test)

Table 4 Laboratory Parameters at Baseline (visit1) and After Treatment Completion (visit 2)

		STB (mg/dL)	SCB (mg/dL)	ALP (Units/L)	γGT (Units/L)	ALT (Units/L)	AST (Units/L)
Overall*	visit 1 (mean [SD])	5.91 (7.18)	3.82 (5.21)	276.51 (159.20)	220.51 (143.97)	105.65 (94.51)	128.83 (99.32)
	visit 2 (mean [SD])	2.72 (2.77)	1.40 (1.65)	203.13 (108.87)	119.19 (57.47)	60.29 (36.20)	64.78 (45.52)
	n (p-value†)	74 (<0.0001)	70 (<0.0001)	67 (<0.0001)	21 (<0.0001)	77 (<0.0001)	74 (<0.0001)
With cirrhosis*	visit 1 (mean [SD])	7.41 (9.76)	4.93 (7.66)	241.66 (107.04)	105.0 (97.86)	65.80 (41.98)	110.67 (80.43)
	visit 2 (mean [SD])	3.32 (2.31)	1.53 (0.92)	242.15 (132.11)	93.67 (93.98)	52.96 (25.26)	67.13 (52.87)
	n (p-value†)	25 (0.0074)	21(0.0023)	21(0.7756)	3 (NA)	26 (0.2125)	25 (0.0270)
Without cirrhosis*	visit 1 (mean [SD])	5.15 (5.38)	3.34 (3.71)	292.42 (176.79)	239.35 (143.28)	125.97 (107)	138.1 (107.28)
	visit 2 (mean [SD])	2.42 (2.96)	1.35 (1.89)	185.31 (92.69)	123.44 (52.08)	64.02 (40.38)	63.58 (41.82)
	n (p-value†)	49 (<0.0001)	49 (<0.0001)	46 (<0.0001)	18 (<0.0001)	51 (<0.0001)	49 (<0.0001)
Heavy drinkers*	visit 1 (mean [SD])	6.80 (8.35)	4.64 (6.08)	293.29 (132.32)	320.88 (224.32)	115.21(110.96)	145.23(112.56)
	visit 2 (mean [SD])	2.87 (3.05)	1.59 (1.95)	212.93 (107.51)	101.49 (68.18)	62.99 (42.29)	68.03 (46.22)
	n (p-value†)	48 (<0.0001)	46 (<0.0001)	44 (<0.0001)	6 (0.0313)	49 (<0.0001)	47 (<0.0001)
Not heavy drinkers*	visit 1 (mean [SD])	4.27 (3.88)	2.24 (2.25)	244.4 (200.43)	179.86 (74.50)	88.92 (52.90)	100.29 (62.84)
	visit 2 (mean [SD])	2.45 (2.19)	1.04 (0.71)	184.37 (111.39)	126.27 (53.57)	55.56 (21.73)	59.12 (44.55)
	n (p-value†)	26 (<0.0001)	24 (<0.0001)	23 (0.0036)	15 (<0.0001)	28 (0.0004)	27 (<0.0001)
Dose 800-1600 mg/day*	visit 1 (mean [SD])	6.35 (7.89)	4.13 (5.74)	282.69 (161.09)	220.15 (143.97)	95.31 (78.02)	122.64 (81.18)
	visit 2 (mean [SD])	2.69 (2.97)	1.42 (1.79)	213.63 (112.54)	119.19 (57.47)	55.95 (29.75)	61.55 (39.27)
	n (p-value†)	59 (<0.0001)	55 (<0.0001)	52 (<0.0001)	21 (<0.0001)	62 (<0.0001)	59 (<0.0001)
Dose <800 mg/day*	visit 1 (mean [SD])	4.17 (2.60)	2.65 (2.12)	255.07 (155.92)	-‡	148.40(139.77)	153.20(152.76)
	visit 2 (mean [SD])	2.85 (1.85)	1.36 (1.04)	166.73 (88.92)	-	78.20 (53.21)	77.47 (64.80)
	n (p-value†)	15 (0.0001)	15 (0.0001)	15 (0.0020)	-	15 (<0.0001)	15 (0.0002)

Abbreviations: ALP = Serum Alkaline Phosphatase, ALT = Serum Alanine Transaminase, AST = Serum Aspartate Transaminase, γGT = Serum γ-Glutamyl Transpeptidase, NA = Not Applicable, SCB = Serum Conjugated Bilirubin, SD = Standard Deviation, STB = Serum Total Bilirubin

*Only the patients with values at both baseline (visit 1) and visit 2 were considered for analysis

†p-values calculated by Wilcoxon signed rank sum test

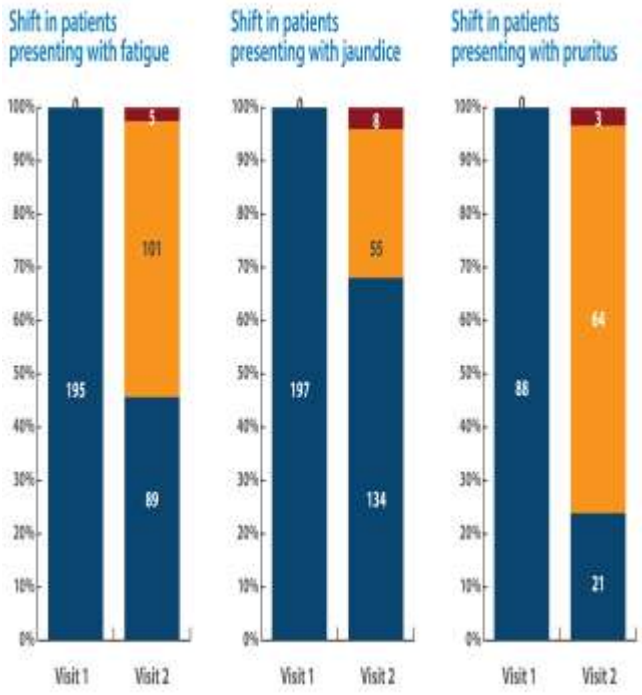
‡There were no patient in this subgroup of dose <800 mg/day with data available for both visits

Signs and symptoms of cholestasis

At baseline, fatigue, jaundice and pruritus were reported by 80.2% (195/243), 81.1% (197/243) and 36.2% (88/243) patients respectively. At visit 2, these proportions decreased to 38% (92/243), 56% (136/243) and 10% (24/243) respectively. A statistically significant ($p<0.05$) shift towards improvement of signs and symptoms was observed in the overall population (Figure 4).

Logistic regression analysis of IHC symptoms and duration of Ademetionine treatment as an independent variable at visit 2 was performed. The odds ratio for IHC symptoms suggested that for one day increase in duration of Ademetionine treatment the chance for presence of IHC symptom of fatigue, jaundice and pruritus decreased by 0.971, 0.997 and 0.895 times respectively, for a patient.

Figure 4: Analysis of Shift in signs and symptoms associated with cholestasis from baseline (visit 1) to visit 2 – Overall, (A) Fatigue, (B) Jaundice, (C) Pruritus



p-values <0.0001 (for all three sign and symptoms,

calculated by McNemar's test)

Overall physician's assessment of Heptral®

Physician's assessment of effectiveness, tolerability and compliance of Ademetionine was based on the data from 193 patients who did not continue Ademetionine treatment post completion of this study. Other 49 patients continued receiving Ademetionine as was decided by the treating physician. Effectiveness was rated as 'very good' and 'good' for 27.5% (53/193) and 72.5% (140/193) patients, respectively. Compliance was rated as 'very good' and 'good' for 29.5% (57/193) and 69.9% (135/193) patients, respectively, and rated as 'bad' for only one patient. Tolerability of the treatment was rated as good or very good for 32.1% (62/193) and 67.9% (131/193) patients, respectively.

Safety assessments

Safety was assessed in the safety population, which consisted of all 250 patients who had received at least one dose of Heptral®. Four (1.6%) patients experienced SAE which resulted in death. The reasons of deaths were reported as cardiac arrest, cardio-respiratory arrest, abdominal pain and pneumonia in these respective patients. All these fatal SAEs were judged as events not related to the study drug by the investigator. No other AE or SAE was observed.

Discussion

The aim of this study was to assess the effectiveness and safety of oral Ademetionine in Indian patients with intrahepatic cholestasis in chronic liver disease due to ALD. This is the first study under the aforementioned settings. The results indicate marked improvement in health-economic parameters due to decrease in number of visits to healthcare services, number of days in hospital and number of days off from work; which essentially result in increased ability to work.

The improvement in biochemical markers, signs and symptoms of cholestasis post Ademetionine treatment observed in our study are in conformity with a previous report by Frezza et al. wherein oral ademetionine (1600 mg/day) for two weeks provided favorable results over placebo [6]. Furthermore in another study treatment with intravenous ademetionine (800 mg/day) for two weeks followed by oral ademetionine (1600 mg/day) for eight weeks demonstrated improvement in biochemical markers (STB, SCB and ALP)[8].
Statistically significant ($p<0.05$) results were found in all biochemical parameters across most subgroups; however, statistical significance could not be

established in the subgroup of patients without concomitant medication because of the small number of patients and the nature of this study being non-interventional, observational.

A meta-analysis by Rambaldi and Gluud was inconclusive about significant clinical effects of ademetionine on chronic liver diseases primarily because it included studies with heterogeneous patient population [9] as well as different formulations of ademetionine (injectable and oral). However, this study has established the clinical effect of Ademetionine in a well-defined patient population, i.e., chronic ALD patients complicated by IHC; which is a major strength of this study.

Substantial proportion (43%) of patients in our study had cirrhosis, a more advanced stage of liver disease. This study included Child-Pugh class A and B patients only because patients with less severe hepatic dysfunction (class A and B) are known to respond satisfactorily to ademetionine treatment, ie, ademetionine being initiated in the earlier phase of disease, and have been documented in earlier studies to be favorable candidates for ademetionine treatment [10]. Patients with Child-Pugh class A and B showed improvement in health-economic parameters and biochemical markers. The study provided an insight into the prescribing patterns of the physicians and took into account their assessment of effectiveness, tolerability and compliance. The physicians' assessment suggested that for all patients, Ademetionine was effective and well-tolerated and most patients were compliant. The SAEs (deaths) reported in this study were judged as not related to Ademetionine by the investigator.

In conclusion, this study provides strong evidence in support of Heptral® use in patients with intrahepatic cholestasis in chronic alcoholic liver disease. Administration of Ademetionine resulted in significant benefit in terms of reduction in health-economic burden (number of days off work, number of visits to healthcare services as outpatient, number of days in hospital), improvement in the levels of biochemical markers and improvement in signs and symptoms of IHC. These beneficial effects of Ademetionine were also seen in all the analyzed subgroups.. Thus, use of Ademetionine offers flexibility as it is effective at varying dosage with patients at different stages of liver diseases with a favorable tolerability and compliance profile.

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List of abbreviations

ALD: alcoholic liver disease, ALP: serum alkaline phosphatase, ALT: serum alanine transaminase, AST: serum aspartate transaminase, γGT: γ-glutamyl transpeptidase, GSH: glutathione, IHC: intrahepatic cholestasis, MedDRA: medical dictionary for regulatory activities, mITT: modified intention-to-treat, PT: preferred term, SAE: serious adverse event, SAMe: *S*-adenosyl-L-methionine, SCB: serum conjugated bilirubin, SD: standard deviation, SOC: system organ class, STB: serum total bilirubin

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