International Journal of Research in Medical Sciences
Saigal S et al. Int J Res Med Sci. 2019 Jun;7(6):2482-2493
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20192550

Review Article

Ademetionine in patients with liver disease: a review

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Received: 09 December 2018
Revised: 02 May 2019
Accepted: 03 May 2019

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ABSTRACT

The aim of the present review is to have an in-depth analysis of the published scientific literature relating to the clinical use of ademetionine in various etiologies of liver disease. Literature search was performed using electronic databases like Pubmed/Medline/others to identify studies on ademetionine in patients with intrahepatic cholestasis, alcoholic liver disease, non-alcoholic fatty liver disease, drug induced liver injury and viral hepatitis. Ademetionine has been studied in various etiologies of liver disease with varying dosing and durations. In patients with chronic and alcoholic liver disease, ademetionine was found to be beneficial in improving liver enzyme levels, increasing glutathione levels, improving signs and symptoms of fatigue, pruritus and jaundice. Positive effects of ademetionine therapy have also been documented in multiple studies in patients with non-alcoholic fatty liver disease, with improvements observed in triglyceride, total cholesterol, alanine transaminase and asprtate transaminase levels and ultrasound grading of fatty change. In patients with drug induced liver injury, improvements were observed in liver biochemical markers and symptoms such as pruritus, fatigue and jaundice. Ademetionine has also been studied in patients with viral hepatitis with improvement in laboratory markers and signs and symptoms. Published data suggest that there is clinical evidence to substantiate the use of ademetionine across indications. Its use has resulted in sustained improvement in biochemical markers; signs and symptoms of liver disease has been observed in both acute and chronic liver disease. Further data is warranted through clinical studies to focus on specific end points of therapy areas, in existing and new indications.

Keywords: Ademetionine, CLD, Cirrhosis, Glutathione

INTRODUCTION

Liver disease is a major cause of illness and death worldwide. This has become a serious public health problem owing to its high prevalence worldwide and poor long-term clinical outcome, including premature deaths from liver decompensation, cirrhosis, and hepatocellular carcinoma (HCC).[1] In spite of advancement in understanding and managing liver disease in the past 30 years, approximately 29 million people in the European region and 30 million people in US still suffer from chronic liver ailments.[2,3] According to the recently available World Health Organization (WHO) data, liver disease deaths in India has reached 216,865, i.e. 2.44% of total deaths. The age-adjusted death rate was 21.96 per 100,000 of population, ranking India 61st in the world.[4] Liver diseases are extremely costly in terms of human suffering, doctor and hospital visits, and premature loss of productivity.

The four major aetiologies contributing to this burgeoning epidemic of liver damage are non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), drug induced liver injury (DILI) and viral hepatitis. Viral hepatitis, excessive alcohol consumption, and obesity are considered the Bermuda triangle for the liver, contributing to liver injury.[5] Based on the etiology, intrahepatic cholestasis (IHC) is present at variable frequencies and in different disease stages in CLD.[6] Clinically, IHC is characterized by the presence of pruritus or jaundice with elevated serum total bilirubin, alkaline phosphatase, and gamma-glutamyl transferase levels.[7]

Alcoholic liver disease

According to WHO, alcohol consumption accounts for 3.8% of the global mortality and 4.6% of disability adjusted life years (DALYs).[8] Liver disease represents 9.5% of alcohol-related DALY's worldwide, while individual rates vary in different regions.[9] In India, alcohol is emerging as the common cause of (CLD).[10] In adult Indian population, the prevalence of alcohol use has been reported to be 21.4%.[11]

The spectrum of alcohol-related liver injury varies from simple steatosis to cirrhosis. It is often grouped into three histological stages namely fatty liver or simple steatosis, alcoholic hepatitis (AH), and chronic hepatitis with hepatic fibrosis or cirrhosis. These are not necessarily distinct stages of evolution of disease, but rather, multiple stages that may be present simultaneously in a given individual.

Patients with fatty liver (steatosis) are usually well and asymptomatic or have nonspecific symptoms and can only be detected by appropriate screening methods.[12,13] They may have slightly elevated liver function test and enlarged liver. Fibrosis is an excessive accumulation of certain abnormal types of protein in the liver, including collagen. It features in most types of CLD. Advanced liver fibrosis results in cirrhosis. Cirrhosis is late-stage liver disease which occurs when scar tissue (fibrosis) replaces healthy tissue. About 10 to 15 percent of people with alcoholism may develop cirrhosis.[14] Clinical jaundice and histological features of IHC may be present in all stages of ALD.

It has been observed that alcohol-attributable liver cirrhosis was responsible for 47.9% of all liver cirrhosis deaths, representing 0.9% of all deaths because of any cause.[15] Deaths from cirrhosis have been estimated to increase, making it the 12th leading cause of death by 2020.[9,16] However, there is a plausibility of underestimation of mortality due to non-documentation of alcohol as the primary cause of death. The lack of specificity of the surveys may also contribute to inaccurate classification of liver diseases. Liver biopsy, while not always necessary, can help to differentiate simple steatosis from steatohepatitis, fibrosis or incipient cirrhosis.[17]

Non- alcoholic fatty liver disease

Worldwide, NAFLD is the most common liver disorder, affecting 20%-40% of population in western countries and about 5%-40% of the general population in the Asia-Pacific region.[18-20] In the United States, it is the most common form of CLD, affecting an estimated 80-100 million people. Guidelines published by the World Gastroenterology Organization suggest that the prevalence of NAFLD has doubled in the last 20 years.[21] The prevalence of the disease is estimated to be around 9-32% in the general Indian population, with higher incidence rate amongst obese and diabetic patients.[22] Two large European studies reported NAFLD prevalence rates of about 42.6–69.5% in samples of adults with type 2 diabetes.[23]

NAFLD, the fatty infiltrations of the liver may sometimes lead to non-alcoholic steatohepatitis (NASH), a more serious stage of the disease where the liver becomes inflamed due to the accumulation of fat. In NASH, fat accumulation is associated with liver cell inflammation and different degrees of scarring. NASH is a potentially serious condition and may lead to severe liver scarring and cirrhosis. About 5% of patients with NAFLD develop cirrhosis.[24] Taken together, IHC ensues in subgroup of patients with NAFLD, providing worse prognosis for advanced disease. Overall, cholestatic features in patients with NAFLD should prompt physicians to rule out the presence of additional (cholestatic) liver diseases.[25]

NAFLD tends to develop in people who are overweight or obese or have diabetes, high cholesterol or high triglycerides. Evidence shows that NAFLD and NASH are the major cause of liver disease in western countries.[21] Rapid weight loss and poor eating habits may also lead to NAFLD. In some patients, fatty liver disease may be accompanied by hepatic inflammation and liver cell death (steatohepatitis).[26] Most people have a better outcome if the condition is detected at an early stage.

Viral hepatitis

Earlier studies have indicated an association between liver cirrhosis and chronic viral hepatitis due to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections.[27-32] HBV and HCV promote cirrhosis; persistent HBV or HCV infection account for over 80% of HCC cases worldwide. The 5-year cumulative risk of developing HCC in patients with cirrhosis ranges between 4% and 30%, depending on etiology, region or ethnicity, and stage of cirrhosis.[33] The prevalence of HBV infection in the overall Indian population is indicated to be about 1-2% and HCV to be about 0.5%-1.5%.[34,35]

The incidence of clinical or laboratory signs of IHC in patients with chronic hepatitis B mostly indicates severe

progressive liver disease or an acute exacerbation of HBV infection. Cholestatic presentation is infrequently seen in chronic HCV infection. Most patients with cholestasis display advanced disease, present with pruritus, and show bile duct injury in the setting of advanced fibrosis.[36]

Drug induced liver injury

Drugs are an important cause of liver injury. More than 900 drugs, toxins, and herbs have been identified to cause liver injury. Drugs account for 20-40% of all instances of fulminant hepatic failure. Approximately 75% of the idiosyncratic drug reactions result in liver transplantation or death. The incidence of DILI is probably higher than the reported range of one in 10,000 to one in 100,000 patients, which may be due to under reporting. Only a minority of drugs have predictable dose-dependent injury.[37,38]

Common signs and symptoms in patients with CLD

Fatigue is the most common and severe symptom reported across etiologies of CLD, including HBV, HCV, NAFLD, and primary biliary cirrhosis (PBC).[39-48] Studies have reported that in patients with NAFLD, fatigue is significantly associated with decreased quality of life (QoL).[49-51] Newton JL et al, observed that fatigue in NAFLD is associated with daytime sleepiness and symptoms of autonomic dysfunction including low blood pressure, though no association was seen with disease severity.[52]

Fatigue is the commonest symptom described by patients with PBC as well and appears to be unrelated to liver disease severity. Fatigue levels has been reported to be consistently higher over a 4-year period in patients with PBC.[53] Severe fatigue and cognitive impairment was reported to be associated with decreased serotonin and dopamine receptor binding in patients with HCV.[54] A trend between higher fatigue scores in individuals with PBC and polymorphism in the CTLA4 gene has also been indicated.[55] Polymorphisms of TRAF1-C5, a member of the tumor necrosis factor receptor family, was reported to be negatively associated with vitality, though association could not be established with fatigue in individuals with PBC.[56]

Pruritus is frequently reported by patients with cholestatic hepatobiliary diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, IHC of pregnancy and hereditary cholestatic syndromes, but may also accompany other liver diseases as well. It is often the major symptom in patients with cholestatic liver disease and can dramatically reduce QoL. Pruritus may be mild and tolerable, but in some, may limit day to day activities and cause severe sleep deprivation resulting in lassitude, fatigue, depression and even suicidal ideation.[57,58] There is an accumulating set of data demonstrating that aspartate aminotransferase (AST) and alanine transaminase (ALT) elevations correlate with morbidity and mortality.[59] Thus it becomes essential that patients' liver enzyme levels along with signs and symptoms are being managed effectively.

Role of ademetionine (S-adenosyl-L-methionine; SAMe) in various liver diseases

As per United States patent application publication, ademetionine1,4-butanedisulphonate (SD4) is a pharmaceutically acceptable stable salt form. The accepted potency levels for S-adenosyl methionine (SAMe, ademetionine) require a minimum of 70% SS (active) isomer content.[60,61] Oxidative stress resulting from excessive accumulation of free radicals and/or their delayed elimination plays a key role in the development of alcoholic liver injury. In liver, S-adenosyl methionine (SAMe, ademetionine), a metabolite of methionine, acts as the methyl donor for all biological methylation reactions, providing the propyl amine group for the synthesis of polyamines, and participating in the synthesis of glutathione (GSH) through the transulfuration pathway. Thus, in liver, ademetionine acts as a precursor of reduced glutathione (GSH), which is a major endogenous antioxidant that protects cells against injury by scavenging free radicals involved in pathogenesis of ALD. Besides its role in restoring hepatic concentration of GSH, ademetionine is thought to provide protection against liver injuries through various other mechanisms. These include (a) attenuation of inflammation by decreasing concentration of pro-inflammatory cytokines such as tumor necrosis factor-α, (b) prevention of apoptosis of hepatocytes and (c) induction of apoptosis of liver tumor cells. There is evidence that ademetionine depletion occurs during CLD. The efficacy of ademetionine in the treatment of liver cell injury has been demonstrated in various experimental animal models.[62-68]

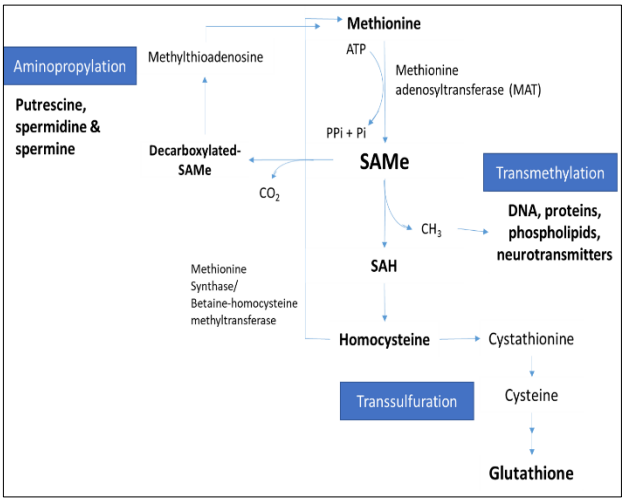

Figure 1: Mechanism of action of methionine.

SAMe is a metabolically pleiotropic molecule that participates in multiple cellular reactions and influences

numerous cellular functions. It is the principle methyl donor required for methylation of nucleic acids, phospholipids, histones, biogenic amines, and proteins.[62-68] Chronic deficiency of ademetionine due to its altered synthesis is associated with cholestasis in hepatitis and cirrhosis.[69]

Liver is the main site for methionine metabolism and SAMe synthesis. In vivo, there are three different ways of SAMe utilization: transmethylation, transsulfuration and amino propylation (Figure 1).[64-68]

Trans methylation reaction

SAMe is a methyl donor and donates methyl group to a number of acceptors like DNA, RNA, proteins, phospholipids etc. Among these, one of the most important transmethylation reaction is the sequential methylation of membrane phospholipids (conversion of phosphatidylethanolamine into phosphatidylcholine). Methylation of membrane phospholipids promotes the fluidity of liver cell membrane and enhances activity of Na+-K+ ATPase which is main driving force for bile secretion and flow. Thus, ademetionine facilitates improved function of hepatocyte membrane-associated bile acid transport systems. Ademetionine participates in the synthesis of a number of substrates: phospholipids, neurotransmitters, nucleic acids, proteins, and porphyrins, as well as in the biotransformation of various drugs.[64-68]

Transsulfuration reaction

Transsulphuration reactions result in the formation of various substances, including the synthesis of glutathione, one of the most important detoxifying agents. The reduction of liver content developing in chronic disorders results in impaired protection of hepatocytes from free radicals as well as endogenous and exogenous substances. Another substance produced with participation of ademetionine, taurine, also plays an important role in the detoxifying function of the liver. Taurine is involved in the bile acid conjugation process. Ademetionine is the precursor of cysteine, taurine, and glutathione.[64-68]

Aminopropylation reaction

In these reactions, the amino propyl group of ademetionine is transferred to polyamines such as putrescine, spermine, and spermidine, which play an important role in ribosomal structure. The synthesis of polyamines is also associated with the process of hepatocyte proliferation. All of that underlies the regenerative (recovering) action of ademetionine. Ademetionine is the precursor of polyamines, such as putrescine (stimulator of cell regeneration and hepatocyte proliferation), spermidine, and spermine, which gets incorporated in the structure of ribosomes.[64-68]

Clinical efficacy of ademetionine in patients with CLD

Ademetionine efficacy and safety has been analyzed in patients with CLD and also with IHC, including patients with alcoholic liver cirrhosis, with beneficial effects of decrease in both laboratory markers and signs-symptoms (fatigue, pruritus) of CLD (Table 1).[70-76]

Frezza M, et al, assessed the effectiveness of ademetionine in cholestatic patients with CLD (ademetionine 1600mg/day versus placebo).[70,71] The results showed that short-term administration (14 days) of oral S-adenosylmethionine was more effective than placebo in improving clinical and laboratory measures of IHC. Therapeutic response to ademetionine treatment for 15 to 30 days was also proved to be superior to placebo, as assessed by resolution of pruritis (77.6% vs 27.8%, $p<0.00001$;OR: 9.23, $p<0.001$), normalization or 50% improvement in serum total bilirubin (65.2% vs 28.6%, $p<0.00001$;OR: 4.69, $p<0.001$), serum conjugated bilirubin (52.3% vs 27.7%, $p<0.00001$; OR: 2.52, $p<0.01$), alanine aminotransferase (52.4% vs 20%, $p<0.00001$; OR: 3.38, $p<0.01$), ϒ-glutamyl transpeptidase (42.9% vs 18.1%, $p<0.00001$; OR: 3.33, $p<0.01$) and alkaline phosphatase (24.1% vs 12.5%, $p<0.01$; OR:1.65).[71] Manzillo G et al, investigated the anticholestatic effect of ademetionine in patients with IHC due to acute hepatitis or CLD.[72] Intravenous ademetionine 800 mg/day (for 14 days) followed by oral ademetionine (1600 mg/day for 56 days) or placebo was the treatment regimen used. Intravenous ademetionine was significantly more effective than placebo in improving pruritus and biochemical abnormalities in IHC and hepatocellular necrosis in patients with CLD and acute hepatitis. Ademetionine treatment seemed to accelerate the recovery from acute hepatitis, as indicated by a greater improvement in serum levels of aminotransferases than that observed with placebo.

The results showed that long term administration of ademetionine in CLD was advisable as oral ademetionine not only maintained the results achieved with intravenous ademetionine but also led to further improvement in liver biochemistry and probably induced a response in patients who had not improved during acute enteral treatment. Perri D et al, assessed the efficacy and tolerability of ademetionine IM (ademetionine (500 mg) for 2 weeks followed by 6 weeks of oral ademetionine (1500 mg/day) on clinical parameters and biochemical markers as well as on QoL in patients with IHC complicating CLD.[73]

Results indicated a significant ($p<0.01$) decrease in total and conjugated bilirubin, alkaline phosphatase, ϒGT, AST and ALT at 2 and 8 weeks of treatment. Short and long-term administration of ademetionine improved clinical and biochemical parameters and QoL score in chronic liver disease patients.

Table 1: Clinical trials evaluating effect of ademetionine on laboratory parameters and signs and symptoms in patients with CLD.

Author	Related disease	Intervention	Duration	Results
Frezza M et al[70]	Cholestatic patients with CLD	Ademetionine (1600mg/day) or placebo	14 days	There was significant decrease in serum markers of cholestasis (p<0.01) and improvement in symptoms such as pruritus, fatigue and feeling of being unwell (P<0.01). Subjective symptoms such as pruritus, fatigue and feeling of being unwell were significantly improved (P<0.01)
Manzillo G et al[72]	IHC due to acute hepatitis and CLD	Intravenous ademetionine 800 mg/day (for 14 days) followed by oral ademetionine (1600 mg/day for 56 days) or placebo	10 weeks	There was significant decrease (p < 0.01) in serum total and conjugated bilirubin, alkaline phosphatase concentrations and pruritus at the end of treatment with oral ademetionine, whereas values in the placebo group were significantly increased (p < 0.01).
Perri DT et al[73]	CLD At baseline, patients presented with Elevated total bilirubin Signs or symptoms Fatigue,itching, jaundice	IM ademetionine (500 mg) for 2 weeks was followed by 6 weeks of oral ademetionine (1500 mg/day) therapy	8 weeks	Significant (p<0.01) decrease in total and conjugated bilirubin, ALP, ϒGT, AST, ALT, pruritus, fatigue and itching was documented at 2 and 8 weeks of treatment
Podymova et al[74]	IHC of CLD	Ademetionine 800 mg/day IV- 16 days followed by 800 mg bid oral (1600 mg/day) 16 days	32 days	There was – decrease in direct bilirubin, GGTP, ALP levels, pruritus, asthenia and jaundice.
Fiorelli et al[75]	IHC of CLD	Ademetionine- 800 mg/d iv or 500mg/d im	15 days	Biochemical response was 61% with SAMe 500 mg IM and 62% with SAMe 800 mg IV. Improvement or disappearance of fatigue and pruritus
Kharchenko et al[76]	IHC Liver cirrhosis was diagnosed in 24.9% of cases	Ademetionine oral and injectable	2 months	Reductions were observed in all main IHC indices: the median of the relative changes of SCB, ALP and GGT was -34.2 %, -22.9 % and -28.2 % at visit1 and these were all approximately doubled at visit 2 (SCB: -60.7%; AP: -44.6%; GGT: -55.0%). More than 80% of patients after two weeks and in 94–96 % of patients after two months of treatment shown improvement.

Clinical evidence of ademetionine use in patients with ALD

Clinical efficacy of ademetionine in cirrhotic patients with ALD

Multiple studies have observed the beneficial role of ademetionine in patients with cirrhosis in ALD, with benefits observed in improvement in liver enzyme levels, increase in levels of glutathione along with improvement in signs and symptoms of fatigue, pruritus and jaundice (Table 2).[69,77-83]

Improvement in survival and laboratory parameters has also been observed in these patients. Mato JM et al, in a randomized, placebo-controlled, double-blind study indicated that long-term treatment with ademetionine may improve survival or delay liver transplantation in patients with alcoholic liver cirrhosis, especially in those with less advanced liver disease.[77] Overall mortality/liver

transplantation at the end of the trial decreased from 30% in the placebo group to 16% in the ademetionine group, (p=0.077). When patients in child C class were excluded from the analysis, the overall mortality/liver transplantation was significantly greater in the placebo group compared with ademetionine group (p=0.025); differences between the two groups in the 2-year survival curves were also statistically significant (p=0.046).

Table 2: Clinical trials evaluating the effect of ademetionine on laboratory parameters, and signs-and symptoms in patients with ALD.

Author	Related disease	Intervention	Duration	Results
Choudhuri G, Singh T[69]	IHC with ALD cirrhosis was present in 42.8% cases	Oral Ademetionine (up to 1600 mg/day)	42 days	There was significant decrease in STB, SCB, ALP, GGT, ALT and AST levels (p<0.0001) as well as 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]) compared to baseline values. Statistically significant (p<0.05) shift towards improvement of fatigue, jaundice & pruritus.
Mato JM et al[77]	Alcoholic liver cirrhosis	Ademetionine- 1200 mg/day, orally) or placebo	2 years	Overall mortality/liver transplantation at the end of the trial decreased from 30% in the placebo group to 16% in the AdoMet group, (p=0.077).
Altomare et al[78]	ALD	1.2 g/d po vs. Placebo	4 weeks or 6 months	Significantly increased hepatic glutathione, cysteine and taurine, reduced methionine
Vendemiale G et al[79]	ALD and non-ALD	Ademetionine- 1200 mg/day, orally) or placebo	24 weeks	Increased hepatic glutathione levels
Corrales et al[80]	Alcoholic cirrhosis	1.2 g/d po vs. Placebo	4 weeks	Improved methionine intolerance with ademetionine
Loguercio et al[81]	40 (20 alcoholic misusers, 20 cirrhotic)	2 g/d iv vs. placebo	15 days	Increased RBC glutathione
Diaz Belmont et al., 1996[82]	ALD	200 mg/d iv vs. Placebo	15 days	Increased plasma glutathione
Chawla et al[83]	Stable alcoholic cirrhosis	800 mg/d iv vs. Placebo	17 days	Total and conjugated serum bilirubin, alkaline phosphatase and transaminases improved.

Effect of ademetionine on signs and symptoms in patients with ALD

Choudhuri G et al, in a post marketing observational study assessed the effectiveness and tolerability of ademetionine 1,4-butane disulfonate in 250 Indian patients presenting with IHC due to chronic ALD.[69] Administration of ademetionine in patients resulted in significant improvement in symptoms, burden of the disease and laboratory markers. In this Indian study, fatigue, jaundice and pruritus were reported by 80.2%, 81.1% and 36.2% patients respectively. A significant (p<0.05) shift towards improvement of signs and symptoms of fatigue, pruritus and jaundice was observed in the cohort population that received ademetionine.

Effect of ademetionine on laboratory parameters in patients with ALD

Multiple studies have indicated the role of ademetionine therapy in increasing hepatic glutathione levels and decreasing liver enzymes including ALT, AST and gamma-glutamyl transferase (GGT) in patients with ALD.

Clinical evidence of ademetionine in patients with NAFLD

Ademetionine has been evaluated in patients with NAFLD, with improvements observed in TG, TC and ultrasound features along with ALT and AST levels (Table 3).[84-87]

Lei MA et al, observed that administration of ademetionine in patients with NASH led to decrease in degree of ALT, AST levels, decrease in TG and TC and normalization of liver ultra-sonogram in 12 cases (60%).[84] Similarly, Baranovsky AYu et al, in his study in NASH patients observed that ademetionine administration caused a decrease in biochemical parameters and trend towards decrease of ultrasonographic liver steatosis.[85]

Table 3: Clinical trials evaluating effect of ademetionine on laboratory parameters and signs and symptoms in patients with non-alcoholic liver disease.

Author	Related disease	Intervention	Duration	Results
MA Lei et al[84]	Non-alcoholic steatohepatitis (NASH)	Diammonium glycyrrhizinate - control group. Intravenous drip of 150 mg ademetionine1,4-butanedisulfonate for injection - once daily for 4 weeks of treatment course.	4 weeks	Decrease levels of ALT, AST, TBil, DBil, yGT was significantly larger than that of control group (P<0.05). TC, TG levels decreased after treatment in ademetionine group (P<0.05). Liver ultrasonogram of 12 cases (60%) in treatment group was reported normal after treatment with ademetionine
Baranovsky AY[85] et al	Nonalcoholic steatohepatitis NASH	•Group-1 - Ademetionine 1200 mg/day PO •Group-2 - Ademetionine 800 mg/day PO •Group-3 - Control	4 months	Trend towards decrease of ultrasonographic liver steatosis grade in the 1st and 2nd groups. Positive changes in anthropometric parameters and hypercholesterolemia severity.
Boming L[86]	Non-alcoholic fatty liver disease	Group1: Ademetionine: (500 mg/ tablet) twice a day for 8 weeks of treatment course. Group 2: Vitamin C	8 weeks	Ademetionine treatment resulted in decrease in TC, TG, ALT and AST levels and improvement in symptoms.
Virukalpattigopalratnam MP et al[87]	IHC due to chronic Non alcoholic liver disease (NALD)	Oral ademetionine	42 days	Ademetionine treatment resulted in statistically significant reduction in levels of STB, SCB, ALP, γGT, ALT, AST (p< 0.05) and signs and symptoms of IHC (p<0.0001). Significant reduction (p < 0.0001) in burden of disease parameters (number of days off work and number of visits to doctor).

Table 4: Clinical trials evaluating effect of ademetionine on laboratory parameters and signs and symptoms in patients with viral hepatitis.

Author	Related disease	Intervention	Duration	Results
Wang Bao-en[88]	Patients with hepatocellular jaundice associated with acute viral hepatitis	Group I (n = 141): Ademetionine (1g) IV OD then oral Ademetionine (0.5g) BD Group II (n = 148): TCR	6 weeks	Ademetionine treatment resulted in significant reduction in serum bilirubin levels compared to TCR at 14, 28, 42and 56 days (p < 0.01). It improved serum transaminases, alkaline phosphatase Genral discomfort and fatigue (p≤0.05).
Feld JJ et al[89]	Nonresponders with Hepatitis C Virus therapy	Ademetionine (1600 mg daily) (n=24)	2 weeks	Second phase slope of viral decline was improved with ademetionine (p=0 .009); 11 patients (53%) achieved an early virological response, and 10 (48%) had undetectable HCV RNA by week 24.

Clinical evidence of ademetionine in patients with viral hepatitis

Ademetionine has also been studied in patients with viral hepatitis (Table 4).[88,89] Bao-en W et al, observed that reduction in serum bilirubin and other laboratory markers was superior with ademetionine compared to traditional Chinese remedy (TCR).[88] Also, the improvement in general discomfort and fatigue was better with ademetionine. Use of ademetionine has also been reported to improve viral response in non-responders with hepatitis C virus therapy.[89]

Clinical evidence of ademetionine in patients with drug induced liver injury

Vincenzi B et al, in 2011 had reported that patients affected by resected colorectal cancer (CRC) and treated with FOLFOX IV adjuvant regimen supplemented with ademetionine had a lower grade of liver toxicity (p= 0.002) and had a reduced need of chemotherapy course delay (p <0.0001), with chemotherapy dose reduction (p =0.031).[90] The AST (p <0.001), ALT (p=0.003), bilirubin (p =0.04) and gamma-glutamyl transferase (g-GT) (p =0.002) median level at the end of adjuvant therapy were significantly lower in patients treated with ademetionine. In this study, 45 patients were given FOLFOX IV without ademetionine and 60 patients were administered the same regimen along with ademetionine (400 mg b.i.d.). Comparable results were obtained in another study in which 42 patients were treated with bevacizumab and XELOX while 32 patients were treated with the same regimen along with ademetionine (400 mg twice in day).[91] Patients supplemented with ademetionine had a lower grade of liver toxicity (P=0.009) and had a reduced need of chemotherapy course delay (P=0.042) and dose reduction (P=0.051) compared with the other group.

In another study, patients were administered ademetionine intravenous/intramuscular 400-800 mg/day, followed by 2 weeks' maintenance treatment (800-1600 mg/day). Post treatment with ademetionine, levels of various laboratory parameters (bilirubin, ALP, γ-glutamyl transpeptidase, ALT, AST) were found to be significantly decreased (p<0.05).[92] Significant improvement in symptoms of IHC such as pruritus, fatigue and jaundice were reported, with a reduction in the number of patients with depressive symptoms (Table 5).[90-93.]

Table 5: Clinical trials evaluating effect of ademetionine on laboratory parameters and signs and symptoms in patients with drug induced liver injury.

Author	Related disease	Intervention	Duration	Results
Vincenzi B et al., 2011[90]	Chemotherapy-induced liver toxicity	45 patients: FOLFOX IV without administering Ademetionine. 60 patients: Same regimen plus supplementation with Ademetionine (400 mg b.i.d.)	Starting from the beginning of chemotherapy program until the end	AST (p < 0.001), ALT (p = 0.003), bilirubin (p = 0.04) and γGT (p = 0.002) median levels at the end of adjuvant therapy were significantly lower in patients treated with Ademetionine. Ademetionine treated patients had a lower grade of liver toxicity (p = 0.002) and had a reduced need of course delay (p < 0.0001) and dose reduction (p = 0.031).
Vincenzi B et al., 2012[91]	DILI	42 patients: bevacizumab and XELOX without administering ademetionine 32 patients: Same regimen plus supplementation with Ademetionine (400 mg twice in day)	Starting from the beginning of chemotherapy program until the end	Biochemical parameters (ALT, AST, LD, TB and GGT) significantly lower in patients treated with ademetionine. Patients supplemented with Ademetionine experimented a lower grade of liver toxicity (P=0.009) and had a reduced need of course delay (P=0.042) and dose reduction (P=0.051).
Santini D et al., 2003[92]	Chemotherapy-induced liver toxicity	Ademetionine: 800mg /d	Between chemotherapy cycles	Significant reduction in ALT and AST at week I (p=0.009 and p=0.0005 respectively) and week II (p<0.0001). Reduction in LDH levels at week 1 and 2 (p=0.012 and p=o.003, respectively)
Perlamutrov, et al., 2014[93]	DILI with IHC induced by immunosuppressive therapy	Start up: Ademetionine intravenous/intramuscular 400-800 mg/day, 2 weeks; Maintenance: 800-1600 mg/day, 4 weeks, orally; Follow up: At end of 4 weeks post-treatment	6 weeks	Post treatment with ademetionine, levels of various laboratory parameters (bilirubin, ALP, γ-glutamyl transpeptidase, ALT, AST) significantly decreased (P< 0.05). Symptoms like pruritus, fatigue and jaundice improved and number of patients with depressive symptoms decreased

CONCLUSION

Much insight has been gained in the epidemiology, pathophysiology and clinical diagnosis of CLD including ALD, NAFLD, DILI and viral hepatitis. Chronic liver diseases such as NAFLD and ALD are a challenge both in primary practice and at specialist level. The armory of therapies presently available, especially in NAFLD and ALD is still very limited. There is a considerable liver disease burden across the world. Considering patients with liver diseases have limited treatment options, this paper has tried to analyze the effects of ademetionine on multiple parameters of liver disease, including laboratory parameters, signs-symptoms of liver disease and ability to tolerate chemotherapeutic drugs.

Ademetionine has been studied in various etiologies of liver disease with varying dosing, and its efficacy has been evaluated at different study durations. In patients with CLD and ALD, studies have noted that ademetionine was beneficial in improvement of liver enzyme levels, increase in levels of glutathione along with improvement in signs and symptoms of fatigue, pruritus and jaundice. The positive effects of ademetionine therapy have been documented in multiple studies in patients with NAFLD, with improvements observed in TG, TC and ultrasound features along with ALT and AST levels. In patients with DILI, improvements were observed in liver biochemical markers and in symptoms of IHC such as pruritus, fatigue and jaundice. Ademetionine has also been studied in patients with viral hepatitis with improvement in laboratory markers and signs and symptoms.

These data suggest that there is substantial clinical evidence of ademetionine and it could offer substantial clinical benefits, including improvement in biochemical markers and in signs and symptoms in patients with CLD. However, further clinical studies are warranted in defined, well-characterized patient groups, focusing on the effects of ademetionine on clinically relevant end points.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. Shalini Nair and Dr. Sanjay Choudhari (Abbott India Ltd.).

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Saigal S, Kapoor D, Roy DS. Ademetionine in patients with liver disease: a review. Int J Res Med Sci 2019;7:2482-93.