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ADEMETIONINE IN TREATMENT OF DRUG INDUCED LIVER INJURY: AN OBSERVATIONAL STUDY IN RUSSIAN PATIENTS, RECEIVING IMMUNOSUPPRESSIVE THERAPY FOR PSORIASIS

Y. Perlamutrov [1], A. Bakulev *[2], I. Korsunskaya[3], E. Orlov [4] and N. Bolotnikova [5]

Moscow State Medical Stomatological University [1], Russia.
Saratov State Medical University [2], Clinic of Dermatology and Venereology Diseases, Russia.
Center of Theoretic Problems Physico-chemistry Pharmacology Russian Academy of Sciences [3], Russia
Samara State Medical University under the Ministry of Public Healthcare and Social Development (Minzdravsocrazvitia) of Russia [4], Russia.
Medical Adviso, Abbott Laboratories [5], Russia.

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Correspondence to Author:
Andrey Bakulev
Professor,
Deputy Chief Physician for the Medical Work at Skin Diseases Clinic, Saratov State Medical University Provianskay st. 22, Saratov, 410028, Russia.

E-mail: al_ba05@mail.ru

ABSTRACT: Background: Drug induced liver injury (DILI), especially; due to use of immunosuppressive agents is a growing concern. Lack of awareness about available treatment options limits its management. This observational study was conducted to characterize Russian population receiving ademetionine as a hepatoprotectant against DILI triggered due to immunosuppressive drugs. **Methods:** A total of 105 patients having DILI with cholestasis (by immunosuppressives) aged 18-65 years were enrolled in a multicentric, non-interventional, prospective observational study. The study had three phases (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). Profiling of patients, reasons for prescribing ademetionine and safety parameters were assessed. Changes from baseline in the levels of laboratory parameters, signs and symptoms of cholestasis and depressed mood were also assessed. **Results:** All enrolled patients were Caucasian (44.4 years; smokers: 41.9%; consumed alcohol daily: 31.4%; history of psoriasis: 86.7%). Methotrexate was the most commonly used immunosuppressive agent (used in 80.0% of patients). Post treatment with ademetionine, levels of various laboratory parameters (bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, alanine transaminase, aspartate transaminase) significantly decreased $P < 0.05$. Symptoms of intrahepatic cholestasis (IHC) such as pruritus, fatigue and jaundice improved and number of patients with depressive symptoms decreased (baseline: 92 [87.6%]; Day 42: 27 [25.7%]). No adverse events were reported. **Conclusions:** In patients with immunosuppressant induced DILI and cholestasis, psoriasis was the most common underlying disorder. Treatment with ademetionine demonstrated beneficial effects in liver disease with improvement in laboratory parameters and symptoms of IHC.

INTRODUCTION: Liver is the target organ for metabolism of most drugs and their direct and indirect effects may lead to hepatotoxicity.

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Drug induced liver injury (DILI) is a growing concern to both scientific and public health community[1]. If left untreated, it can present a significant challenge, ranging from increased incidence to its effect on morbidity and mortality. One of the most severe manifestations of DILI is intrahepatic cholestasis (IHC) accounting for more than half of the reported cases of hepatotoxicity[2]. It is generally associated with fatigue, pruritus and jaundice; asymptomatic patients may also have

elevated serum levels of alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γ GT) [2-4].

DILI induced by immunosuppressants needs specific attention as they are widely used in the treatment of various diseases such as psoriasis. The primary challenge of managing DILI is its late diagnosis as many patients may remain asymptomatic for longer period of time, leading to substantial progression of the disease and ultimate delay in its treatment. Till date, limited options are available for DILI management. General practice is to withdraw the drug that is thought to have caused liver injury and to provide supportive treatment with hepatoprotective drugs to alleviate the symptoms of chronic liver injury[1, 3].

Various processes like oxidative stress, hepatocellular apoptosis and mitochondrial membrane dysfunction are involved in the pathogenesis of cholestasis[5]. Drug induced cholestasis may occur due to changes in the expression of the enzymes or transporters involved in these pathways or reduced hepatic concentrations of glutathione. S-adenosyl-L-methionine (ademetionine) serves as a principle methyl donor for methyltransferase reaction essential for generation of glutathione which helps in reducing the toxicity of free radicals generated by various agents including immunosuppressive agents[6, 7].

Thus, providing external supplements of ademetionine may prove beneficial in patient with diminished liver reserves[7, 8]. Favorable effects of ademetionine on improvement in biochemical parameters and sign and symptoms of IHC such as fatigue and pruritus have been demonstrated in several clinical studies[8-11].

Although beneficial effects of ademetionine are known, there is lacuna of information about ademetionine prescribed to DILI patients induced by immunosuppressive therapy. The present non-interventional, Prospective, multicenter, observational study was conducted to characterize the Russian patients with DILI caused due to immunosuppressive therapy and to aid physician's decision making in its management. In addition, reasons for prescribing ademetionine were assessed. Other objectives included evaluation of effectiveness of ademetionine therapy in these patients and to explore correlation between laboratory parameters and sign and symptoms of liver disease.

METHODS:

Study Design

This was a multicenter, non-interventional, prospective, observational study conducted from July 2011 to April 2012 at nine sites in Russian Federation. The total duration of study was 10 weeks and consisted of start-up (2 weeks), Maintenance (4 weeks) and a Follow up (4 weeks) phase. It had four scheduled visits. The protocol was approved by the independent ethics committee at each study site and the study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

Patients

Out-patients, men and women aged 18-65 years with DILI induced by immunosuppressive therapy were enrolled in the present study. All patients with DILI had intrahepatic cholestasis and were treated with ademetionine as per locally approved label. Patients with hepatocellular or metastatic liver carcinoma, severe liver disease including but not limited to ascites, hepatic encephalopathy, hypoalbuminemia and coagulopathy were excluded from the study. Other exclusion criteria included women who were pregnant (1^{st}-2^{nd} trimester) and lactating and patients contraindicated to ademetionine treatment (including hypersensitivity) according to the local label. All patients provided written informed consent to participate in the study.

Treatment

All enrolled patients were initially treated with intravenous or intramuscular ademetionine 400 to 800 mg daily for 2 weeks (Start-up Phase) followed by oral maintenance therapy of 800 to 1600 mg daily for 4 weeks. Safety follow-up was continued till 30 days after the last administration of ademetionine.

Study assessments

The primary variables included assessment of demographics, baseline characteristics, underlying

liver disease and reasons for prescribing ademetionine.

Secondary variables were change in laboratory investigations (bilirubin [total, conjugated], alkaline phosphatase [ALP], γ glutamyl transpeptidase [γ GT], alanine transaminase [ALT] and aspartate transaminase [AST]) from baseline to end of 6 weeks. Sign and symptoms of cholestasis and depressed mood were documented by the investigators based on the questionnaires filled by the patients.

Signs and symptoms of cholestasis (jaundice, fatigue, pruritus) were assessed on the basis of two degree score (0=absent, 1=present), and for depressed mood a four degree score was used (0=absent, 1=mild, 2= moderate, 3=severe). Exploratory analysis was conducted to evaluate the association between laboratory values and sign and symptoms of liver disease.

Safety

Investigators monitored the patients for occurrence of any adverse event. Safety was evaluated by assessment of adverse events.

Approximately 100 patients was planned to be enrolled in the study this was an observational non-comparative study, statistical analyses were of descriptive in nature. For all measurements, the final value obtained before the administration of ademetionine was used as the baseline value. Continuous data (e.g. age, changes in laboratory parameters from baseline) were presented as mean ± SD and categorical data (e.g. gender, race) were summarized using frequencies and percentages. Patients with depressed mood were compared using Chi-Square test. Exploratory endpoints including association between laboratory values or sign and symptoms of liver disease were analyzed using Spearman's correlation coefficient. All tests were two-sided and performed at 5% significance level.

RESULTS:

Primary Variable

Demographics and Baseline Characteristics

All enrolled patients (N=105) completed the study. All patients were Caucasian and had a mean age of 44.4 years (range 18 to 65 years). Of the total enrolled patients, 41.9% were smokers and 31.4% consumed alcohol daily. Patient's demographics are presented in **Table 1**.

TABLE 1: DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF PATIENTS

Variables	Ademetionine N=105
Sex, n (%)	
Men	53 (50.5)
Women	52 (49.5)
Age (years), mean ± SD	
Men	40.6 ±9.8
Women	48.3 ± 12.4
Race, n (%)	
Caucasian (white)	105(100.0)
Smoker, n (%)	
Yes	44 (41.9)
No	61 (58.1%)
Daily alcohol consumption, n (%)	
Yes	33 (31.4)
No	72 (68.6)
Frequency of alcohol consumption, n (%)	
1-3 drinks/day	26 (24.8)
4-6 drinks/day	7 (6.7)

Hepatobiliary disorders reported among the patients are presented in **Figure. 1**.

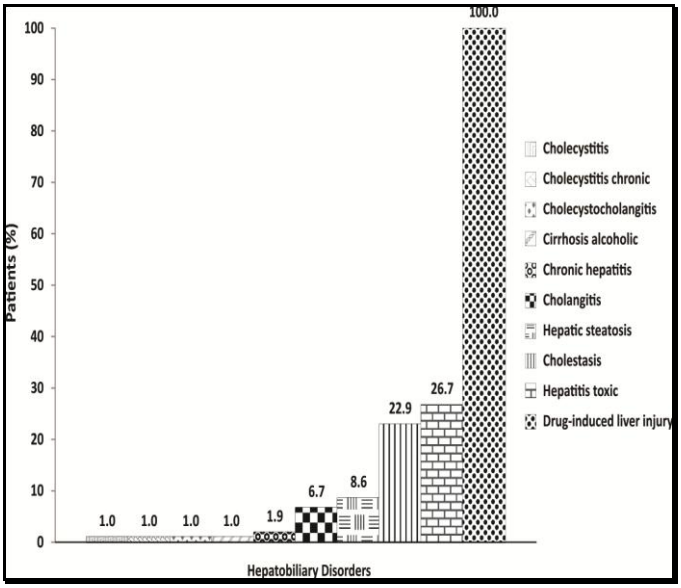

FIGURE 1: HEPATOBILIARY DISORDERS AMONG THE STUDY PATIENTS

Skin and subcutaneous disorders (90.5%) were other most common conditions reported by patients (Psoriasis: 86.7%, Psoriatic arthropathy: 17.1%). Other disorders were gastrointestinal (5.7%), infections and infestations (5.7%), metabolism and

nutrition (1.9%), psychiatric (1%) and surgical procedures (6.7%).

Drugs causing DILI and concomitant medication

An immunosuppressive agent (94.3%) was the most common class causing DILI followed by corticosteroids (11.4%) for systemic uses **(Figure. 2)**. Methotrexate (80%) was the most frequently used concomitant medication followed by vitamin B1 in combination with vitamin B6 and/or vitamin B12 (19.0%), and psycho stimulants and nootropics (13.3%).

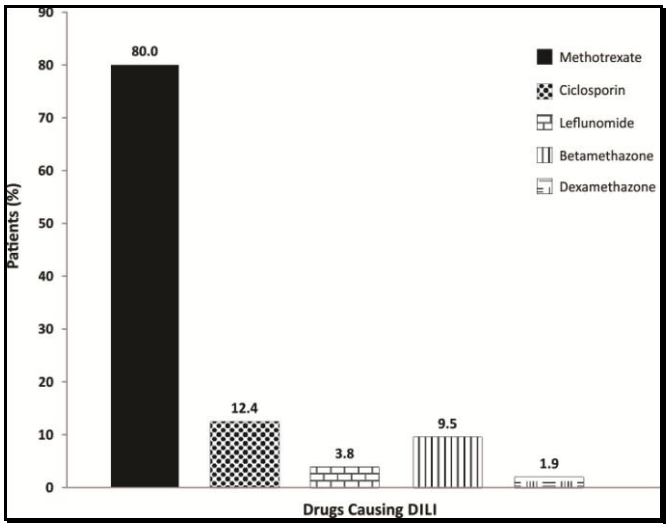

FIGURE 2: DRUGS CAUSING DILI IN STUDY PATIENTS

Reasons for Prescribing Ademetionine

All patients were prescribed ademetionine, the most common reasons being DILI (79 patients [75.2%]) followed by cholestasis (24 patients [22.9%]) and toxic hepatitis (3 patients [2.9%]).

Secondary Outcomes

Laboratory parameters

At the end of the observation period of 6 week, significant reduction from baseline was reported in laboratory parameters (total bilirubin, conjugated bilirubin, ALP, γ-GT, ALT and AST) (P<0.05) **[Figure.3 (A-C)]**.

Signs and symptoms of IHC

At baseline, pruritus and fatigue (both in 85 patients [81.0%]) were the most commonly reported symptoms of IHC followed by jaundice in 21 patients (20.0%). At day 42, the patients reporting pruritus, fatigue and jaundice decreased to 7(6.7%), 12(11.4%) and 2(1.9%), respectively. The number of patients reporting no symptoms of jaundice, pruritus and fatigue were 2 (1.9%) at baseline which increased to 90 (85.7%) on day 42. **(Figure.4A)**.

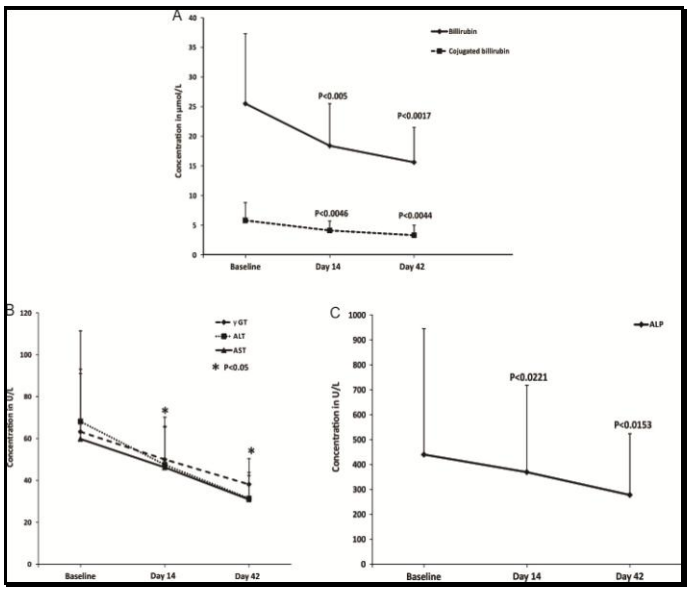

FIGURE 3: THE MEAN CHANGE FROM BASELINE TO THE END OF 6 WEEKS AFTER TREATMENT WITH ADEMETIONINE A) TOTAL BILIRUBIN AND CONJUGATED BILIRUBIN LEVELS, B) Γ-GLUTAMYL TRANSPEPTIDASE (ΓGT), ALANINE TRANSAMINASE (ALT), ASPARTATE TRANSAMINASE (AST) LEVELS, C) ALKALINE PHOSPHATASE (ALP) LEVELS

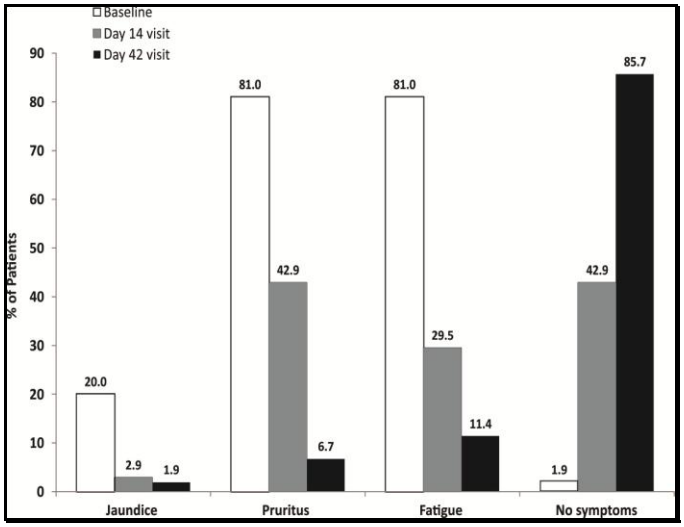

FIGURE 4A: PERCENTAGE OF PATIENTS EXHIBITING SYMPTOMS OF IHC AT BASELINE AND AFTER TREATMENT WITH ADEMETIONINE

Depressed mood

Percentage of patients with depressed mood (mild, moderate and severe) at baseline, day 14 and day 42 is depicted in **Fig.4B**. At baseline 13 (12.4%) patients were without depressed mood. This

number increased to 53 (50.5%) on day 14 and on day 42, as high as 78 patients (74.3%) were without depressed mood (P<0.001) **(Figure.4B)**.

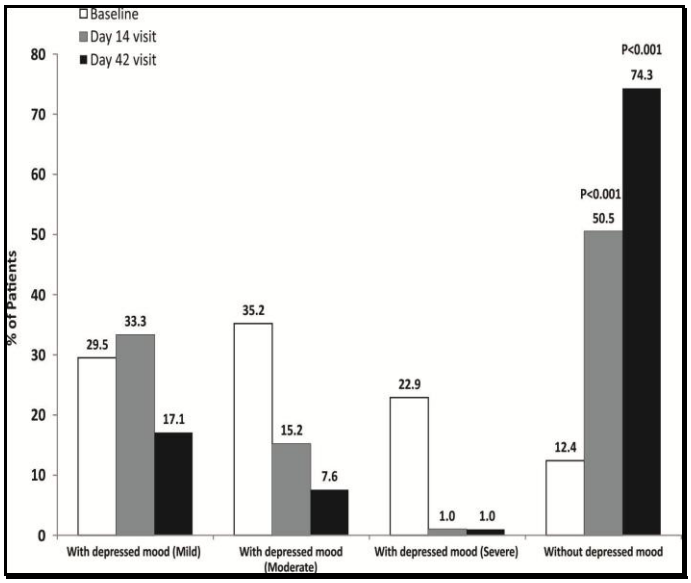

FIGURE 4B: PERCENTAGE OF PATIENTS WITH SEVERITY OF DEPRESSED MOOD AND THOSE WITHOUT DEPRESSED MOOD AT BASELINE AND AFTER TREATMENT WITH ADEMETIONINE

Exploratory Variables:

All pairs of ALP, γ-GT, ALT and AST exhibited statistically significant (P<0.0001) positive correlation between changes from baseline to day 42 visit. Further, clinical symptoms such as pruritus and fatigue decreased with decrease in the laboratory parameters (ALP, γGT, ALT and AST) (P<0.05). Clinical symptoms like (jaundice, pruritus, fatigue and depressed mood) also exhibited significant positive correlation between themselves (P<0.05).

Safety Results:

There were no adverse events reported throughout the study.

DISCUSSIONS: Increasing incidence of DILI and its progression towards acute liver failure and fatality needs attention by medical care system. Due to increased identification of hepatotoxicity of several prescription drugs and associated serious adverse effects, the management of the toxic effects has gained equal importance as the treatment of the malady itself. Difficulty in diagnosis due to wide spectrum of DILI and lack of the treatment options, affects decision making process of physician in its management.

To address this, an observational study was conducted to characterize a target Russian population receiving ademetionine as a hepatoprotectant against DILI triggered due to immunosuppressive drugs.

In this study, psoriasis was found to be the most common underlying disorder (86.7 %). Psoriasis, is often treated with immunosuppressive drugs like methotrexate, cyclosporine, leflunomide or fumaric acid; and is known to be frequently associated with liver diseases and other serious life-threatening comorbidities[12-14]. Relationship between the use of immunosupressives and the development of hepatic abnormalities has been documented in clinical and observational studies[13, 15, 16]. Long-term treatment with these drugs in psoriatic patients may further accelerate liver toxicity and limit their benefits. Hence, drug prescription for severe psoriasis treatment requires careful understanding of patient characteristics.

Among the immunosuppressives, methotrexate is the most widely used drug for the treatment of psoriasis[13, 15]. Similarly, in the present study, methotrexate was prescribed in majority of the patients (80.0 %) followed by cyclosporine (12.4%) and leflunomide (3.8%). Hepatotoxicity of immunosupressives in patients with psoriasis appears to increase with the dose, duration of treatment and is associated with generation of free radicals and is manifested in the form of elevation of serum enzymes, progressive fibrosis and cirrhosis[13, 15, 16]. Ademetionine by increasing the production of glutathione counters the toxicity of free oxygen radicals generated by various toxins such as immunosuppressive agents [7, 11]. This may suffice the reason for prescribing ademetionine in the present study.

Ademetionine has a proven hepatoprotective function in liver injury. The same was demonstrated in the present study and even with the concomitant use of immunosuppressive drugs there was decrease in values of laboratory markers such as total bilirubin, ALP, ALT, AST, γGT and improvement in symptoms of IHC such as jaundice, fatigue and pruritus. While the other studies[10, 17]did not correlate the clinical symptoms of IHC and the related laboratory parameters, our study showed a strong correlation between them.

Clinical symptoms (pruritus and fatigue) of liver disease decreased with the decrease in the laboratory parameters suggesting a correlation between them. Findings of improvement in signs and symptoms of IHC are consistent with previous studies wherein ademetionine was administrated to patients during immunosuppressive treatment [10, 17]. This suggests that the use of ademetionine along with the hepatotoxic drugs may prove to be beneficial in improving the clinical signs and biochemical parameters in patients with liver diseases.

Further, psoriasis not only affects the patient's physical health but is also associated with emotional and social consequences. Several studies reported that psoriatic patients have increased risk of depression and anxiety[14, 18, 19]. The present study demonstrated decrease in the symptoms related to depression and severity of depression in patients after treatment with ademetionine. This can be attributed to ademetionine's anti-depressant activity that has been reported in few studies[17, 20, 21].

Ademetionine is well tolerated and its safety has been established from several clinical trials and post-marketing experience. In a long-term study conducted by Mato et al. in cirrhotic patients, no severe adverse events were reported with ademetionine treatment[8]. Similarly, Frezza et al. demonstrated that treatment with ademetionine was well-tolerated and only mild and transient side effects were recorded in a few cholestatic patients with chronic liver disease[9]. In line with these studies, there were no adverse events reported and no physician stopped ademetionine treatment due to lack of efficacy. These results also correspond with typical reporting pattern in routine medical practice in Russia.

CONCLUSIONS: Dealing with DILI is important. In the present study, psoriasis was the most common underlying disorder for which immunosuppressive was prescribed in patients with DILI and cholestasis. Treatment with ademetionine demonstrated beneficial effects with decrease in laboratory parameters related to liver disease and improvement in symptoms of IHC. The number of patients with symptoms of depression and the severity of depressed mood decreased. Encouraging results of the present study in Russian patients with chronic liver disease after ademetionine treatment may facilitate physicians in decision making process.

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