Original Article

A Retrospective, Multi-Center, Post-Marketing Observational Study to Evaluate the Effectiveness of Ademetionine 1,4-Butanedisulfonate Injection (Transmetil®) Treatment in Chinese Patients with Intrahepatic Cholestasis Caused by Viral Hepatitis

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Objective Ademetionine 1,4-butanedisulfonate [S-adenosyl-L-methionine (SAME)/Transmetil®, Abbott] has been available in China for more than 15 years, and it has been shown to reduce serum bilirubin and transaminase levels in viral hepatitis (VH) patients. However, no large-scale studies have focused on the impact of SAME treatment regimen on reducing the serum total bilirubin (TBil) in VH patients with intrahepatic cholestasis (IHC). The primary purpose of this study was to evaluate the effectiveness of intravenous SAME (Transmetil®) treatment in reducing the serum TBil by 50%.

Methods This retrospective, multi-center, cross-sectional medical record review involved patients aged ≥ 18 years. Records of 1 280 hospitalized VH patients at 16 sites diagnosed with IHC who had received intravenous SAME 1 000 mg or 2 000 mg q.d. for at least 7 days from January 1, 2006 to June 30, 2009, were screened and 905 records were randomly selected.

Results The safety set (SS) included 834 patients and the full analysis set 826 patients. TBil levels after 14 days injection treatment were available for 763 patients. TBil decreased $\geq 50\%$ versus baseline after 14 days treatment in 288 (37.7%) patients (95% CI 34.3%, 41.2%). Twenty-nine non-serious adverse events (non-SAEs) were reported in 19 (2.3%) patients, and 29 SAEs were reported in 10 patients (1.2%). All adverse events (AEs) were considered unrelated to the study drug.

Conclusions This retrospective study shows that intravenous SAME administration in VH patients with IHC is associated with significant reduction of TBil levels in more than 30% of patients 14 days after treatment initiation.

Key words: Ademetionine 1,4-butanedisulfonate; Intrahepatic cholestasis; Viral hepatitis

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Viral hepatitis (VH) is one of the leading causes of liver disease worldwide. Populations in the far east nations of Asia are highly endemic for HBV infection. In the People's Republic of China, nearly 10% of the population was HBsAg-positive before fully funded government vaccination programs started in 2003.¹ Infection with HEV among the elderly and during pregnancy often leads to intrahepatic cholestasis (IHC) and in some cases to liver failure.

Most VH patients have abnormal liver functions, characterized by high levels of serum total bilirubin (TBil), alkaline phosphatase (ALP), γ -glutamyl transpeptidase (GGT), bile acids (BA) and transaminases.

Ademetionine 1,4-butanedisulfonate [S-adenosyl-L-methionine (SAdMe)/Transmetil[®], Abbott] was launched in China over 15 years ago and clinical data show that it is effective in reducing serum bilirubin and transaminase levels in VH patients.^{2,3} However, large scale studies focusing on the impact of ademetionine on reducing serum levels of TBil, BA and transaminases do not exist.

This retrospective analysis of approximately 900 cases intends to describe the effectiveness of intravenous ademetionine in reducing serum TBil, BA, GGT, ALT and transaminase levels among Chinese VH patients with IHC.

METHODS

This was a retrospective, multi-center, patient medical chart review. Baseline data, laboratory data and AEs occurring during treatment were recorded.

Objectives

The primary objective was to evaluate the effectiveness of ademetionine injection treatment in reducing serum TBil by 50% among patients with IHC due to VH. The secondary objectives were to evaluate 1) the speed and extent of reduction of serum TBil, ALP, GGT, BA and transaminase levels; 2) whether or not the reduction of these laboratory measurements were maintained and 3) the safety profile of ademetionine injection.

Patient population

Inclusion and exclusion criteria

Patients were included in the study if they were: 1) male or female, age ≥ 18 ; 2) diagnosed as IHC due to hepatitis per local diagnosis criteria for VH (positive serum virus marker for HBV and/or HEV) and IHC (serum total and conjugated bilirubin and BA levels more than 2 times upper limit of normal (ULN));

canalicular enzymes (ALP and/or GGT) more than 2 times ULN; 3) have been treated with ademetionine injection for at least 7 days.

Exclusion criteria

The exclusion criteria were: 1) grade II or more severe hepatic encephalopathy; 2) a history of alcoholic dependency within 1 year before SAdMe treatment; 3) pregnancy or lactation; 4) use of artificial liver support; 5) glucocorticoid use.

Outcome measures

Effectiveness

Primary and secondary endpoints

The primary endpoint is the percentage of the patients who achieved a 50% decrease in serum TBil after 14 days of treatment with ademetionine.

Secondary endpoints include 1) the percentage of patients who achieved a 50% decrease in serum TBil from baseline levels after each week treatment; 2) percentage of patients who had normalization of serum TBil levels, 30% decrease of ALP levels or normalization of ALP levels, 3) speed and extent of reduction of serum TBil, BA, ALP, GGT and transaminase (alanine transaminase or ALT and aspartate aminotransferase or AST) levels; 4) maintenance of the reduced serum TBil, BA and transaminase levels.

Safety

Safety endpoints include: 1) the incidence of AEs; 2) abnormal and clinically significant laboratory results; 3) 12-lead- electrocardiogram (ECG).

Statistics

Sample size

Sample size calculation was based on the difference between pre- and post- treatment levels of TBil, ALP, GGT, BA and transaminases. For the primary endpoint, 30 subjects were enough to detect a difference. The largest sample size requirement to detect a difference was for GGT among the secondary endpoints. Assuming a difference 22.4 U/L GGT between baseline and 14 days of treatment and a standard deviation (SD) of 155.2 U/L, 600 patients would provide 90% power to detect a difference using the paired *t*-test, at $\alpha=0.05$. To account for exclusions to the eligibility criteria, 1 200 records were screened, among which records would eventually be randomly selected. A post hoc subgroup analysis was performed to examine other variables of interest. Subgroups were compared using site-adjusted Cochrane-Mantel-Haenszel (CMH) test

for categorical and ANCOVA for continuous variables. General linear models (GLM) were used to explore colinearity of several variables with laboratory outcome parameters.

Safety

Incidence (%) of AEs were analyzed according to the guideline issued by the State Food and Drug Administration (SFDA) of China. Seriousness and causal relationships were also tabulated.

RESULTS

Study flow

This was a retrospective, multi-center, patient medical chart review study, thus independent ethics committee review and approval was required only for one site. Sites were initiated between November 2009 and July 2010. A total of 1 280 medical records of patients seen from Jan 1, 2006 until Jun 30, 2009, in 16 sites distributed in 12 big cities of China, were screened. Patient numbers were recorded on the screening sheet separately by site, then the statistician selected records using simple random sampling from each site. In total, 905 records were included and information was extracted onto case report forms (CRFs) which was completed in Sep., 2010. After review of CRFs, 71 of 905 patients were found not to meet inclusion and exclusion criteria thus not meeting the criteria of safety set (SS). There were 834 patients in the SS and 826 patients in the FAS (full analysis set). TBil levels after 14 days injection treatment were available for 763 patients, thus these were included in the analysis of

primary endpoint (Figure 1).

Demographics

Demographic characteristics of the SS are summarized in Table 1. Majority of patients were male (682 or 81.8%), and were ethnically of Han nationality (815 or 97.7%). The average age $\pm$ SD of the patients was 48.09 ± 13.63 years, with age ranging from 18 to 85 years. Among these patients, 129 (15.5%) cases were diagnosed as HEV infection only.

Demographic data of the FAS are summarized in Table 1 showing similar results as in the safety set.

Baseline description of effectiveness parameters

Descriptive statistics of all baseline effectiveness parameters of FAS are shown in Table 2. The patients had significant liver dysfunction before treatment with ademetionine, with mean values for each parameter above the normal range. Mean TBil level was high at 215.67 ± 146.02 μ mol/L, approximately $11 \times$ ULN. The mean value of ALP was $1.3 \times$ ULN, GGT was $3.1 \times$ ULN, BA was more than $16 \times$ ULN.

Effectiveness results

Primary endpoint

The percentage of patients whose serum TBil decreased by $\geq 50\%$ from baseline after 14 days treatment in FAS was 37.7% (288/763), with 95% CI 34.3%-41.2%.

In order to elucidate the relationship of baseline serum TBil with response rate, a post hoc analysis was conducted. The patients were grouped according to the level of their baseline serum TBil: group 1 (19.9% or 39/196 of patients) had TBil $< 5 \times$ ULN; Group 2

Figure 1. Study flow chart.

Table 1. Demographic data of SS and FAS

SS data		FAS data	
Gender n (%)		Gender n (%)	
Male	682 (81.8%)	Male	677 (82.0%)
Female	152 (18.2%)	Female	149 (18.0%)
Nation n (%)		Nation n (%)	
Han	815 (97.7%)	Han	807 (97.7%)
Others	19 (2.3%)	Others	19 (2.3%)
Age (years)		Age (years)	
Mean $\pm$ SD	48.09 $\pm$ 13.63	Mean $\pm$ SD	48.00 $\pm$ 13.63
Median	49	Median	49
Min, Max	18, 85	Min, Max	18, 85
Etiology n (%)		Etiology n (%)	
HEV only	129 (15.5%)	HEV only	127 (15.4%)
Others	705 (84.5%)	Others	699 (84.6%)
Total	834 (100%)	Total	826 (100%)

Table 2. Baseline description of effectiveness parameters of FAS

Parameters	Normal Range (from site 1)	Number of cases (missing cases)	Mean $\pm$ SD	Median	Min-Max
TBil (μ mol/L)	0.0 - 18.8	826 (0)	215.67 $\pm$ 146.02	180.00	12.20 - 710.41
ALP (U/L)	42.0 -141.0	750 (76)	178.36 $\pm$ 155.69	145.25	37.00 - 3 197.10
GGT (U/L)	7.0 - 49.0	768 (58)	152.22 $\pm$ 160.87	101.95	10.00 - 1 824.00
BA (μ mol/L)	0.0 - 10.0	627 (199)	165.98 $\pm$ 134.10	148.70	1.60 - 1 737.00
ALT (U/L)	0.0 - 40.0	825 (1)	447.22 $\pm$ 642.85	164.00	4.50 - 4 926.00
AST (U/L)	0.0 - 40.0	800 (26)	338.96 $\pm$ 466.28	153.00	17.00 - 4 478.00

Table 3. The percentage of patients whose serum TBil decreased $\geq$ 50% versus baseline after 14 days treatment in FAS – grouped by baseline serum TBil

Group number	Baseline serum TBil	Number of patients	Percentage of serum TBil decreased $\geq$ 50% versus baseline after 14 days treatment (number of patient/total number of patient)	95% CI	P value
1	< 5 $\times$ ULN	196	19.9% (39/196)	14.3%-25.5%	
2	$\geq$ 5 $\times$ ULN and <10 $\times$ ULN	245	45.3% (111/245)	39.0%-51.6%	vs. group 1 < 0.001
3	$\geq$ 10 $\times$ ULN and <20 $\times$ ULN	238	44.5% (106/238)	38.2%-50.9%	vs. group 1 < 0.001
4	$\geq$ 20 $\times$ ULN	84	38.1% (32/84)	27.5%-48.7%	vs. group 1 0.003

(45.3% or 111/245 of patients) had TBil $\geq$ 5 $\times$ ULN; group 3 (44.5% or 106/238 of patients) had TBil $\geq$ 10 $\times$ ULN with and < 20 $\times$ ULN and group 4 (38.1% or 32/84 of patients) had TBil $\geq$ 20 $\times$ ULN (Table 3).

The percentage of patients whose serum TBil decreased by 50% or more after 14 days of treatment were all significantly higher in groups 2, 3 and 4 when compared to those in group 1 ($P < 0.01$). The proportion of patients responding in groups 2 (45.3%), 3 (44.5%) and 4 (38.1%) were similar (Figure 2).

A post hoc analysis with dosage subgroups (1 000 mg and 2 000 mg daily) was also conducted to further describe the association of treatment dosage with response. In the 1 000 mg group, 38.4% (95%

CI 34.7-42.1%) of patients (253/659), had a decrease in serum TBil of $\geq$ 50% after 14 days treatment and in the 2 000 mg group, it was 33.7% (95% CI was 24.4%-42.9%) of patients (253/659). The difference in response between these two subgroups was not significant ($P = 0.164$) (Table 4).

Analysis of the association of drug combinations with response rate was also performed. The top three reported drug combinations were chosen: group 1, SAME/glycyrrhizin preparation/thiol donor; group 2, SAME/glycyrrhizin preparation; group 3, SAME/glycyrrhizin preparation/Chinese anti-icteric medicine / thiol donor.

Combinations were used at least once in 94.3%

Figure 2. The percentage of patients whose serum TB decreased $\geq 50\%$ versus baseline after 14 days treatment in FAS – grouped by baseline serum TB ($P = 0.902$).

Notes: The relationship between serum TB decrease and baseline serum TB. All patients were grouped by baseline serum TB: $\geq 5 \times \text{ULN}$, $\geq 10 \times \text{ULN}$, $< 20 \times \text{ULN}$, $\text{TB} \geq 20 \times \text{ULN}$, respectively. The percentage of patients whose serum TB decreased $\geq 50\%$ versus baseline after 14 days treatment were calculated in every group and differences between groups were analysed by Student t test.

Figure 3. The percentage of patients whose serum TB decreased $\geq 50\%$ versus baseline after 14 days treatment in FAS – grouped by the most commonly used combination treatment.

Notes: The association of different drug combinations treatment with response rate. All patients were grouped by the most commonly used combination treatment: SAME/glycyrrhizin preparation/thiol donor, SAME/glycyrrhizin preparation, SAME/glycyrrhizin preparation/Chinese anti-icteric medicine /thiol donor, respectively. The percentage of patients whose serum TB decreased $\geq 50\%$ versus baseline after 14 days treatment were calculated in every group and differences between groups were analysed by Student t test.

Table 4. The percentage of patients whose serum TBil decreased $\geq 50\%$ versus baseline after 14 days treatment in FAS – grouped by dose of ademetionine

Treatment dose (mg)	Number of patients	Percentage of serum TBil decreased $\geq 50\%$ versus baseline after 14 days treatment (number of patients/total number of patients)	95% CI	P value*
1 000	659	38.4% (253/659)	34.7%-42.1%	0.164
2 000	104	33.7% (35/104)	24.4%-42.9%	

* Based on site adjusted CMH test

(779/826) of patients in the FAS. Group 1 combination was used at least once by 9.4% (73/779), group 2 combination by 9.2% (72/779); and group 3 combination, by 8.1% (63/779). The percentages of patients in each subgroup with a decrease in serum TBil of $\geq 50\%$ versus baseline were 50.0% (33/66), 48.5% (32/66) and 48.3% (28/58), respectively, and the differences were not significant ($P = 0.888$) (Figure 3).

Subgroup analysis of the association of treatment

duration (7 and 14 days) with response was also performed. Among those treated for 7 days, the percentage of patients whose serum TBil decreased $\geq 50\%$ was 14.8% (95% CI, 12.1%-17.5%) or 98/664 patients and after 14 days treatment it was 37.7% (95% CI 34.3%-41.2%) or 288/763 patients.

Secondary endpoints

The category of subgroups was the same as category for primary endpoint analysis.

Figure 4. The percentage of patients whose serum TB decreased $\geq 50\%$ versus baseline by weekly in FAS- grouped by baseline serum TB.

Notes: All patients were grouped by baseline serum TB as described in Figure 2. The percentage of patients whose serum TB decreased $\geq 50\%$ versus baseline were calculated weekly until week 8. After 8 weeks treatment, differences between groups were analysed by Student *t* test.

Table 5. Maintenance percentage of laboratory parameters one week after discontinuing ademetonine treatment

Laboratory parameter	n (N = 826)	% (95% CI)	Subgroups with significant associations (<i>P</i> value)*
ALT	768	93.0 (91.2, 94.7)	Baseline TBil (0.01)
AST	765	92.6 (90.8, 94.4)	Baseline TBil (0.002)
TBil	794	96.1 (94.8, 97.4)	Baseline TBil (0.002)
ALP	747	90.4 (88.4, 92.4)	Treatment dose (0.038)
GGT	758	91.8 (89.9, 93.6)	Baseline TBil (0.001)
BA	755	91.4 (89.5, 93.3)	None

* Four subgroup analyses were performed: association according to baseline TBil, treatment dose, drug combinations, treatment duration.

Weekly results of percentage of serum TBil decreased $\geq 50\%$ versus baseline in FAS

The percentage of patients whose serum TBil decreased $\geq 50\%$ versus baseline was evaluated every week, and this increased each week throughout the duration of treatment in the FAS. After 8 weeks of treatment, the percentage of patients in group 1 (baseline TBil $< 5 \times \text{ULN}$), whose serum TBil decreased $\geq 50\%$ versus baseline was significantly lower than that of other subgroups ($P < 0.05$) (Figure 4). There was no difference between subgroups based on dose, the most commonly used drug combinations and treatment ($P > 0.05$).

Percentage and median time of normalization of serum TBil and/or 30% ALP decrease from baseline or normal ALP at least once in FAS

During the treatment period, 56.2% (95%CI was 52.8%-59.6%) of patients (464/826) achieved normal serum TBil and/or 30% ALP level reduction from baseline or normal ALP levels at least once. Median time for normalization was 14 days, with the mean and SD of 15.99 ± 9.58 days and a range of five to 79 days. The mean number of days to achieve these laboratory characteristics were not significantly different in the subgroup analyses by baseline serum TBil, drug combinations and treatment dose.

Maintenance percentage of laboratory parameters 1 week after stopping treatment in the FAS

The maintenance percentage was defined as the percentage of patients whose laboratory parameters were either maintained or improved seven days after discontinuing the treatment (Table 5). More than 90% of patients maintained or reduced each of their laboratory parameters. Baseline TBil levels were associated with maintenance of AST, ALT, TBil and GGT, but not with that of ALP and BA. ALP maintenance was the only one associated with treatment dose. Maintenance percentages for any of the laboratory parameters were not associated with treatment duration nor treatment combinations.

Simple regression model for time and measurement on each time point in FAS

Simple regression analyses were performed to describe the relationship between treatment duration (week) and mean laboratory parameters (serum TBil, ALP, GGT, ALT, AST and BA levels). Negative regression coefficients were reported for all parameters.

The regression coefficient for serum TBil was -8.736 ($F = 15.535$, $P = 0.002$). TBil decreased over treatment time. In the subgroup analysis by baseline TBil, higher levels were correlated with faster reduction ($F = 3.667$, $P = 0.019$, regression coefficients were negative).

Table 6. GLM to test the association between the extent of reduction of observed effectiveness parameters on day 14 and independent variable (FAS)

Parameters	Source of variations	Standard regression coefficient	<i>t</i> value	<i>P</i> value
TBil	HBV	-0.103	-2.729	0.007
	Baseline TBil	0.453	11.763	<0.001
	Baseline ALP	-0.114	-3.091	0.002
	Baseline BA	-0.110	-2.862	0.004
	Baseline ALT	0.120	3.176	0.002
ALP	HBV	-0.087	-2.475	0.014
	Baseline TB	-0.079	-2.291	0.022
	HEV	29.399	2.106	0.036
	Baseline ALP	0.502	14.491	<0.001
GGT	Baseline GGT	0.731	25.744	<0.001
BA	HBV	-0.060	-2.144	0.032
	Treatment dose	-0.065	-2.412	0.016
	Glycyrrhizin	0.060	2.191	0.029
	Thiol donor	-0.057	-2.095	0.037
	UDCA	-0.106	-3.953	<0.001
	Antiviral treatment	-0.068	-2.379	0.018
	Baseline GGT	0.054	2.005	0.045
	Baseline BA	0.714	26.261	<0.001
	Baseline ALT	0.132	4.738	<0.001
	HBV	-0.019	-3.833	<0.001
ALT	Baseline TB	-0.017	-3.426	<0.001
	Baseline ALT	1.009	128.323	<0.001
	Baseline AST	-0.025	-3.166	0.002
	HBV	-0.033	-4.260	<0.001
AST	Baseline TB	-0.036	-4.732	<0.001
	Baseline ALP	-0.029	-3.847	<0.001
	Baseline ALT	0.047	3.846	<0.001
	Baseline AST	0.942	76.480	<0.001

Table 7. Summary of AE (SS)

	Number of AEs	Number of patients (Incidence %) N = 834
Total number of non SAEs	29	19 (2.3)
Relationship to pharmaceutical product		
Probably related	0	0 (0.0)
Possibly related	0	0 (0.0)
Possibly not related	9	6 (0.7)
Not related	18	14 (1.7)
Unknown	2	1 (0.1)
Total number of SAEs	29	10 (1.2)
Total number of SAEs related to pharmaceutical product	0	0 (0.0)
Deaths	10	10 (1.2)
Liver failure	8	8 (1.0)
Hepatitis, hepatorenal syndrome, acute heart failure and acute respiratory failure	1	1 (0.1)
Upper gastrointestinal hemorrhage, hemorrhagic shock and respiratory failure	1	1 (0.1)

GLM for the degree of reduction and explanatory variables

General linear models (GLM) were used to explore possible factors that are correlated with reduction of

laboratory parameters associated with liver disease after 14 days of ademetionine treatment (Table 6). In this exploratory analysis, hepatitis B status is consistently negatively correlated with reduction in all laboratory parameters at 14 days except GGT. Hepatitis E status has a strong positive correlation with ALP reduction at 14 days with $\beta = 29.399$ ($P = 0.036$).

Safety results

Twenty-nine non-serious adverse events (AEs) were reported by 2.3% of the patients (19/834) in the safety set. Of these, 27 were reported to be unrelated to the treatments and for two the causality was unknown (Table 7). There were 5 patients who reported “jaundice aggravated” (0.6%).

Ten patients (1.2% or 10/834) experienced 29 SAEs. They all died during treatment but their deaths were attributed to underlying conditions and were deemed unrelated to ademetionine (Table 6).

DISCUSSION

Cholestasis is an impairment of bile formation and/or bile flow which may cause clinical symptoms and abnormal liver function tests.⁴ IHC has previously been defined as a greater than 2 folds increase in various parameters such as serum total bilirubin (TBil), CBil and ALP.^{5,6} Most recently, the 2009 EASL clinical practice guidelines for management of cholestatic liver diseases have proposed ALP greater than 1.5 ULN and GGT greater than 3 ULN for early diagnosis.⁷ In this study, IHC was defined as serum TBil, CBil and BA exceeding twice the ULN or canalicular enzymes (ALP and/or GGT) exceeding twice the ULN. Interestingly the mean value of ALP was only 1.3 times ULN and of GGT 3.1 times ULN even when the mean value of TBil was more than 10 times ULN. This underscores the importance of routinely measuring ALP and GGT rather than simply relying on hyperbilirubinemia to demonstrate the presence of IHC. Although the value of BA is not mentioned in the EASL guidelines, the mean baseline value of BA in this study was more than 16×ULN. This finding merits further exploration of BA levels as a possible additional screening test for ICH, and examining the correlation between TBil and BA may provide additional information in future studies.

The administration of ademetionine appears to be related to reduction of TBil levels in this retrospective review of Chinese patients with viral hepatitis. More than one third (37.7%) of the patients with IHC caused by VH (HBV and/or HEV infection) had a reduction

of 50% or more in serum TBil after 14 days treatment with intravenous ademetionine injections. Normal serum TBil levels or 30% ALP decrease from baseline or normal ALP was achieved at least once during the review period in 56.2% of patients. The average time for normalization in these patients was 14 days. For all the baseline parameters observed, such as TBil, ALP, GGT, BA and transaminases, longer treatment duration was associated with a more prominent reduction.

This study suggests that ademetionine treatment in HBV and HEV patients correlates with improvement of routine laboratory indicators of hepatic disease, and are consistent with findings from other studies done among IHC patients with hepatitis.^{2,5,6} Comparative exploratory clinical studies also demonstrated a biological effect of SAME on hepatitis C,^{8,9} but none so far on hepatitis E. However, in the present study, all patients received ademetionine, thus it is not possible to ascertain whether the trend in the outcome is due to ademetionine, other treatments, disease natural history or other confounding or effect-modifying factors.

Baseline TBil appears to be strongly correlated, as reduction in TBil was higher after ademetionine treatment if the baseline TBil was also higher ($> 5 \times \text{ULN}$).

An analysis of association of dosage showed that the response was not different between those receiving 1 000 mg compared to 2 000 mg. However, secondary analysis shows that among all parameters, only maintenance of ALP levels was significantly associated with dosage one week after stopping treatment. This finding is consistent with the clinically expected effect of ademetionine since ALP is a recognized parameter to estimate cholestasis.

HBV/HEV status was observed to be associated with reduction of laboratory parameters after 14 days of treatment. HBV positive status was negatively correlated with all parameters except GGT although the coefficients were relatively small. Thus HBV positive status is correlated with a negative reduction, i.e. a small increase in these parameters after 14 treatment days. HEV positive status was positively correlated with ALP, a known predictor of IHC. Data suggest HEV positive patients are likely to have a 29 unit reduction in ALP after 14 treatment days, after controlling for baseline variables. This suggests that some parameters are more likely to be deranged in certain conditions and responses of these parameters to ademetionine are variable.

Ten patients died during the data collection period but these were attributed to the progression of disease

as they were in later stages of liver failure.¹⁰⁻¹²

Comparison of the most commonly used treatment combinations showed that combinations with three or more drugs were not significantly more beneficial than those with less drugs. The effectiveness of using combinations of different hepatoprotectors in Chinese routine clinical practice should probably be re-examined.

Ademetionine or SAME is formed from essential amino acid methionine and adenosine triphosphate (ATP) in a reaction catalyzed by methionine adenosyl transferases (MAT). Its metabolites such as phosphatidylcholine improves fluidity of cell membranes. SAME also participates in glutathione generation thus promoting bile acid intake and biliary excretion.¹³⁻¹⁵ Studies show that SAME and its metabolite 5-methylthioadenosine play a role in inflammation through regulating IL-10 and increasing synthesis of IL-6 in the liver.¹⁶⁻²¹ SAME deficiency occurs in many forms of liver disease, and could ultimately lead to the development of fatty liver and potentially to sensitization to TNF-induced hepatotoxicity.²²

This is a retrospective observational study in a cohort of viral hepatitis patients with IHC who all received ademetionine, and is prone to bias and confounding. All attempts were made to avoid selection bias by using statistically simple random sampling by site. Relationships between associated factors including baseline variables, treatment variations and outcomes of interest are exploratory in nature and causality will require further investigations to elucidate. It is important to recognize that this study, despite its limitations, is the first large investigation of HBV and/or HEV patients with IHC treated with intravenous ademetionine and other concomitant drugs.

Pre-clinical evidence supports the physiological roles of SAME in health and various liver diseases may affect these.²³ SAME also appear to influence diverse hepatocellular processes including oxidative stress, mitochondrial function, apoptosis and malignant transformation. Clinical studies in hepatitis C suggest that its role goes beyond improving IHC.²²⁻²³ SAME could potentially offer substantial benefits, however few high-quality trials exist. Future well-designed, prospective studies are needed, incorporating learning from existing data including those from exploratory studies such as this. By addressing these, the therapeutic potential of SAME can be translated from bench to the bedside.

ACKNOWLEDGEMENTS

The current study was sponsored by Abbott China.

Wen Xie and Jun Cheng thank their colleagues at Beijing Ditan Hospital who assisted in patient enrollment and also thank their peers from other 15 sites for patient enrollment.

The following centers in China participated in the study: 1) Beijing Ditan Hospital, Capital Medical University, Beijing; 2) Beijing YouAn Hospital, Capital Medical University, Beijing; 3) Shanghai Public Health Clinical Center, Shanghai; 4) Tianjin Infectious Disease Hospital, Tianjin; 5) Dalian Sixth People's Hospital, Dalian; 6) Ningbo No.2 Hospital, Ningbo; 7) The 302 Military Hospital of China, Beijing; 8) West China Hospital of Sichuan University, Chengdu; 9) Fuzhou Infectious Diseases Hospital, Fuzhou; 10) Xuzhou Infectious Diseases Hospital, Xuzhou; 11) The First Affiliated Hospital of Jilin University, Changchun; 12) Huaian Chuzhou Hospital, Chuzhou; 13) China-Japan Friendship Hospital Affiliated to Jilin University, Changchun; 14) Yangzhou Third people's Hospital, Yangzhou; 15) The First Affiliated Hospital of Soochow University, Soochow; 16) Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai.

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